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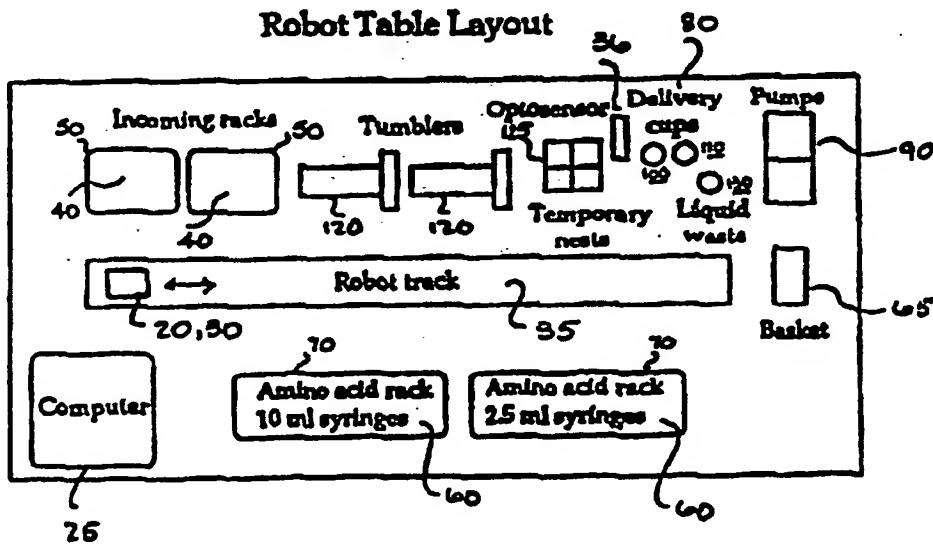
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(54) Title: APPARATUS AND METHOD FOR MULTIPLE SYNTHESIS OF ORGANIC COMPOUNDS ON POLYMER SUPPORT

10



(57) Abstract

A solid phase synthesis system is provided by employing a fully automated robot (20) that operates with a novel timing protocol executed by a computer (25) for handling multiple synthetic tasks efficiently. The fully automated robot (20) moves along a track (35) and is equipped with a gripper arm (30) which can pick up, position, and operate syringes (40, 60) which can contain solid supports and amino acid reactants. The novel timing protocol is realized by performing steps in the synthesis cycles for different compounds, such as peptides, concurrently rather than on a sequential basis.

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APPARATUS AND METHOD FOR
MULTIPLE SYNTHESIS OF ORGANIC
COMPOUNDS ON POLYMER SUPPORT

5 Technical Field

This invention relates to an apparatus and method for the multiple synthesis of compounds consisting essentially of repeating structural units formed, for example, by repeated washing, deprotection, and 10 coupling. More particularly, the invention is directed to a system for the multiple synthesis of organic compounds, such as peptides, which uses an automated robot for handling multiple synthetic tasks.

15 Reference To Microfiche Appendix

A microfiche appendix consisting of two (2) microfiches and of a hundred twenty (120) frames is included as a part of the specification. The microfiche appendix contains a program listing 20 implementing the present invention. The program listing is subject to copyright protection. The copyright owner, however, has no objection to the facsimile reproduction by anyone of the program listing, as it appears in the Patent and Trademark 25 Office file or records, but otherwise reserves all copyright rights whatsoever.

Background of The Invention

Systems for the synthesis of organic compounds, 30 for example peptides, are highly desired for many applications. For example, the synthesis and collection of a large number of peptides would assist in the development of agents that could block, promote or otherwise affect cellular reactions that involve 35 recognition and binding. These agents would be useful in the treatment or diagnosis of a number of diseases.

More particularly, synthetic peptides can be used as diagnostic and therapeutic agents.

Understandably, peptide synthesis systems have been designed and constructed. Houghten, R.A., Proc. Natl Acad. Sci., 82: 5131-5135 (1985), employs a "tea bag" method using standard Boc amino acid resin in polypropylene mesh packets with standard washing, deprotection, neutralization, and coupling protocols of the original solid phase procedure of Merrifield, R.B., J. Amer. Chem Soc., 85: 2149-2154 (1963).

Although some peptide synthesis systems have been automated for the synthesis of multiple peptides, they generally exhibit poor "respite" time, unable to handle efficiently multiple synthetic tasks. For example, commercial peptide synthesis systems, such as those from Gilson, USA and Advanced Chem Tech, are capable of synthesizing multiple peptide sequences. However, these automated synthesis systems perform each step in the synthetic cycles for all peptides one by one or sequentially. The timing protocol, more specifically, involves washing all peptides one by one, deprotecting all peptides one by one and then coupling all peptides one by one. For example, coupling is initiated for a first peptide and then when those first initiation coupling steps are completed, coupling is initiated for a second peptide. Such a timing protocol results in an especially long delay or respite time between peptide synthesis steps. Washing all peptides one by one is time consuming. Moreover, during coupling, the system is idle while waiting for coupling to finish. With coupling taking up to 2 hours, the efficiency of prior art automated synthesis systems is severely limited.

Furthermore, prior art automated peptide synthesis systems critically lack flexibility. Once the synthesis of a peptide set has started, any additional peptides, even those urgently required, 5 cannot be started. Furthermore, prior art systems lack the flexibility so as to execute more than one type of coupling reaction, which is typically required for the synthesis of non-peptide compounds.

10 Summary of The Invention

A novel synthesis system overcoming the drawbacks of the prior art is realized by employing a fully automated robot that operates with a novel timing protocol for handling multiple synthetic tasks 15 efficiently. The novel timing protocol is realized by performing different steps in the synthesis cycles for multiple organic compounds concurrently rather than on a sequential basis.

20 Advantageously, this novel timing protocol provides the flexibility of readily adding desired compounds to the list of compounds to be synthesized, changing the order in which the compounds are synthesized, or deleting previously entered compounds.

25 More importantly, such a timing approach or protocol decreases the "respite" time - new synthesis steps of the next compound synthesis being initiated prior to the completion of those in the previous synthesis.

30 In an exemplary embodiment, the novel synthesis system includes an industrial robot system operating under computer control for effecting the synthesis steps within each cycle of the selected compounds, for example, peptides. Each synthetic cycle comprises 35 five different steps: washing, adding deprotection

reagents, deprotection, adding coupling reagents and coupling. Because deprotection and coupling do not involve any robot action they are passive synthetic steps, although chemically active; the other steps are 5 active synthetic steps.

Importantly, the novel timing protocol is realized by having the robot system, during the passive synthetic steps of a compound synthesis, 10 perform active synthetic steps for the synthesis cycle of the synthesis of the next compound.

In a preferred embodiment of the invention, a solid-phase peptide synthesis is used, with a first 15 set of plastic syringes containing the resin used as the solid support and serving as the reaction vessel. Additionally, a second set of plastic syringes contains amino acids. The robot system equipped with a gripper arm positions any one of the plurality of 20 syringes to selectively aspirate and dispense solvents and reagents from the desired syringe in accordance with the novel timing protocol for coupling predetermined amino acids to the solid support.

25 Brief Description of The Drawings

A more complete understanding of the invention may be obtained by reading the following description in conjunction with the appended drawing in which like elements are labeled similarly and in which:

30 Fig. 1 is a block diagram of a synthesis system in accordance with the principles of the invention;

Figs. 2A and 2B are illustrative flow charts representing the operation of the synthesis system of Fig. 1, and more particularly, the timing protocol; 35 and

Fig. 3 is a chart illustrative of the timing protocol for the synthesis system of Fig. 1.

Detailed Description

5 The invention relates to an apparatus for the multiple synthesis of compounds consisting essentially of repeating structural units, for example peptides, formed by repeated washing, deprotection, and coupling. The apparatus or synthesis system employs a
10 fully automated robot system that operates with a novel timing protocol for handling multiple synthetic tasks efficiently. The novel timing protocol is realized by performing different steps in the different synthesis cycles of multiple organic
15 compounds concurrently rather than on a sequential basis, as discussed in more detail below.

Without any loss of generality or applicability for the principles of the present invention, the
20 overall operation of the present invention is described using, as an example, Fmoc/tBu chemistry, applied to the Merrifield solid phase synthesis of peptides. It should, however, be understood that the present invention is equally applicable to any other
25 chemistry for the solid phase synthesis of compounds that consist essentially of repeating structural units, such as polymers or organic compounds as described, for example, in Borchardt et al., J. Am. Chem. Soc., 116: 373 (1994); Chen et al., J. Am. Chem. Soc., 116: 2661 (1994); Simon et al., PNAS, 89: 9367 (1992); Nikolaiev et al., Pept. Res., 6: 161-70 (1993); and Lebl et al., Vol. 5: 541-548, Techniques In Protein Chemistry, Academic Press, San Diego (1994), which are incorporated herein by reference.

Before describing the present invention, however, it will be instructive to discuss briefly the basic principles of peptide synthesis. Peptide synthesis involves the coupling of amino acids and may be 5 accomplished by techniques familiar to those skilled in the art. See, for example, Stewart and Young, Solid Phase Synthesis, Second Edition, Pierce Chemical Co., Rockford, IL (1984), which is incorporated herein by reference.

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The process of peptide synthesis on solid supports generally involves building a peptide from the carboxyl or C-terminal end in which the C-terminal amino acid with its protected α -amino group is 15 attached to a solid phase polymer. The protecting group is then cleaved off, and the next amino acid, also protected, is coupled by a peptide bond to the α -amino group of the amino acid attached to the solid support. The cycle of deprotecting the prior amino 20 acid and coupling the additional amino acid is repeated until the desired peptide is synthesized. Any reactive side chains of the amino acids are protected by chemical groups that can withstand the coupling and $\text{N}\alpha$ -deprotection procedure. These side 25 chain protecting groups, however, can be removed at the end of the synthesis.

In order to couple an amino acid to the growing synthetic chain, the carboxyl group of the blocked 30 amino acid must be activated. Many methods of activation may be used, including, for example, preformed symmetrical anhydrides (PSA), preformed mixed anhydride (PMA), acid chlorides, active esters, and *in situ* activation of the carboxylic acid.

35

The present synthesis system includes a fully automated robot system interfaced to a computer for effecting the synthesis cycle of each desired peptide to be synthesized. Referring to Fig. 1, there is 5 illustrated a block diagram of a preferred embodiment of a system for the multiple synthesis of compounds, more particularly peptides, applying standard Fmoc/tBu chemistry in accordance with the principles of the invention.

10

Synthesis system 10 comprises an industrial robot system 20, such as Model A251 from CRC Plus, Inc., Harrington, Canada, that is interfaced to a IBM personal computer 25. Computer 25 includes such 15 hardware as a central processing unit, program and random access memories, timing and control circuitry, input and output interface devices, and other digital subsystems necessary to the operation of the central processing unit, all of which are well known and 20 understood in the art. Accordingly, such computer hardware is not discussed herein for the sake of clarity.

Robot system 20 is programmed to effect different 25 mechanical manipulations through the use of pre-programmed steps typically provided for in software programs delivered with the robot system. Alternatively, such preprogrammed steps can be provided for in third party software programs, such as 30 Total Control For Windows, Hudson Control Group Inc., Springfield, New Jersey. Those skilled in the art will readily note that other computer means, microcomputer control means or other automated control means, including other programming software, may be

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alternatively provided to effect mechanical manipulations.

Automated robot system 20 equipped with a gripper 5 arm 30 that is movable under program control along track 35 can pick up and position (X,Y,Z) any one of a plurality of syringes to any predetermined location. The gripper arm is used to selectively aspirate and dispense solvents and reagents from the desired 10 syringe which serves as the reaction vessel for coupling predetermined amino acids to a solid support. More particularly, each syringe has a plunger that is movable by the gripper arm so as to aspirate or dispense reagents in a manner well known to those 15 skilled in the art. See, for example, Krchnak, V., Vagner, J., "Color-Monitored Solid-Phase Multiple Peptide Synthesis Under Low-Pressure Continuous Flow Conditions," Peptide Res. 3, 182 (1990), which is incorporated herein by reference. Moreover, the 20 gripper arm provides a means for shaking the contents of the syringes. Also, the content amount of reagents in each syringe can be readily determined by detecting the position of the plunger within the desired syringe. Also, to confirm that the syringe has been 25 properly gripped and positioned, an optical sensor 36 detecting the motion of the syringes is preferably used to provide feedback to the synthesis system.

A suitable solid support may be selected, such as 30 a polystyrene or polyethylene glycol/polystyrene resin. The protected amino acids may be readily obtained from a number of places, such as Bachem (Torrance, California), Advanced ChemTech (Louisville, Kentucky) or Propeptide (Vert-le-Petit, France).

Importantly, computer 25 also controls when each step in the synthesis cycle is initiated so as to implement the novel timing protocol of the present invention wherein different steps in the synthesis 5 cycles of multiple peptides are performed concurrently rather than on a sequential basis.

More particularly, synthesis system 10 includes a first set of plastic syringes 40 for holding resin 10 used as the solid support, herein referred to as "resin syringes." In the preferred embodiment, RAM-TentaGel (0.21 mmol/g) obtained from Rapp-Polymer, Tubingen, Germany, is used as the resin.

15 First set of plastic resin syringes 40 is placed in incoming racks 50, each holding up to, for example, thirty 10 ml and thirty 2.5 ml syringes. Synthesis system 10 also includes a second set of plastic syringes 60 for holding amino acid solutions, herein 20 referred to as "amino acid syringes." Similarly, second set of syringes 60 are placed in racks 70, each holding up to, for example, a hundred 10.0 ml and a hundred 2.5 ml syringes. Basket 65 holds the completed synthesized peptides. The number and size 25 of the first and second sets of syringes will be dependent on the number of different peptides synthesized, the length of the peptides and the number of different amino acids required.

30 Plastic syringes 40, 60 preferably are made of a material, such as polypropylene, that is sufficiently chemically inert to all solvents and reagents used in the solid-phase peptide synthesis, including trifluoroacetic acid. Alternative materials include 35 Kevlar, Teflon or cast glass.

Each plastic resin syringe 40, which serves as the reaction vessel, is equipped at the bottom with a frit (not shown). It should be understood that various other vessels and means for retaining the 5 solid phase and removing the excess reagents and solvents may be used. For example, columns or wells fitted with a frit or filter may be used as alternative reaction vessels that are compatible with the present synthesis system. In that alternative, 10 the columns or wells are connected to a vacuum source in such a manner that they can be disconnected from the reaction vessel. Moreover, the frit or the means for retaining the solid phase does not have to be integral with the reaction vessel. Rather, it can be 15 external or only present when necessary to retain the solid phase during the removal of solution therefrom.

Appropriate solvents and reagents are introduced from solvent reservoirs to delivery cups 80 using four 20 10 ml piston pump systems 90, such as the Hamilton MicroLab 900, Reno Nevada. Commercial-grade solvents and reagents, such as dimethylformamide (DMF), piperidine/DMF, DIC/DMF, are used. Three of the piston pumps deliver solvents and reagents to delivery 25 cups 80 whereas the fourth piston pump removes waste as well as wash solution from cups 80 where the amino acids and the coupling reagents are mixed.

Delivery cups 80 comprise a first cup 100 that is 30 used for all washing and for receiving the protected amino acids and coupling reagents, and a second cup 110 that is used for receiving deprotection reagents.

Those skilled in the art will readily note that 35 further independent manipulating stations may be used

to manipulate the syringes, depending on the particular reaction desired therein, such as dispensing, aspirating, shaking, heating, cooling or even refluxing. In those instants, robot 5 system 20 would only be required to position the appropriate syringes in the desired manipulating stations. This would decrease the required time to perform the active synthetic steps because the most time consuming tasks would be distributed among 10 multiple and independent manipulating stations.

Using the above synthesis system, multiple peptides are synthesized by manipulating the syringes so as to repeatably attach during a synthetic cycle a 15 desired amino acid to the solid support. Those skilled in the art will note that there is neither a physical link, such as tubing and valves, between the reagent vessels and the reaction vessels nor between the mixing chambers and the reaction vessels. As 20 such, different reagents and reaction conditions may be used within the same or different peptide synthesis.

Each synthetic cycle consists of the following 25 sequence of basic operations or steps: washing, adding deprotection reagents, deprotection, adding coupling reagents, and coupling. Judiciously combining synthetic cycles, each coupling a desired amino acid, creates a synthesis protocol for the synthesis of the 30 desired peptide. Only three of the above synthetic steps, washing, adding deprotection reagents and adding coupling reagents, however, directly require the use of robot system 20. These steps are referred herein to as "active synthetic steps," although

chemically passive, and are discussed in more detail below.

During washing, robot system 20 positions a selected resin syringe from rack 40, a tumbler 120 or holding position 125 and then dispenses any liquid therein into liquid waste 130. A preprogrammed amount of washing liquid is subsequently delivered to first cup 100 using piston pump system 90 and then aspirated together with a preprogrammed amount of air using the selected resin syringe. Robot system 20 finally then shakes the selected resin syringe for a preprogrammed time to ensure efficient mixing.

15 Adding deprotection reagents similarly requires the use of robot system 20. Robot system 20 positions the desired resin syringe over liquid waste 130 and dispenses any liquid therein. A preprogrammed amount of deprotection mixture is subsequently delivered to 20 second cup 110 and then aspirated together with a preprogrammed amount of air using the selected resin syringe.

Lastly, adding coupling reagents also requires the use of robot system 20. Robot system 20 positions the selected resin syringe in holding position 125. Robot system 20 then selects and positions a selected amino acid syringe, dispensing a predetermined amount of desired amino acid into first cup 100. The 30 selected amino acid syringe is repositioned in rack 40. A preprogrammed amount of activating agents is then delivered to first cup 100 and aspirated together with a preprogrammed amount of air using the selected resin syringe located in holding position 125. That 35 selected resin syringe is then positioned into tumbler

120. Next, robot system 20 dispenses a preprogrammed amount of washing solvent into first cup 100 which is then aspirated. Typically, the latter steps of tumbling and washing are repeated a number of times, 5 preferably three times.

During deprotection and coupling, the syringes are placed on 2.5 ml or 10.0 ml tumbling racks 120, each of which holds up to 18 syringes, to ensure an 10 efficient mixing.

In order to better understand the timing protocol that allows the handling of multiple synthetic tasks more efficiently, a discussion of the underlying basis 15 for the timing protocol would be instructive, particularly with reference to the flow charts of Figs. 2A and 2B.

To begin with, the user enters the sequence of 20 compounds to be synthesized. And, if the necessary reagents are available, the system will start to initiate a desired synthesis - otherwise, the user is notified of the deficiencies. More particularly, for 25 each desired synthesis, the system determines the particular synthetic steps, both active and passive, that are required to synthesize the sequence as well as determines when those synthetic steps are to be performed - that is, their timing or temporal relationship within the synthetic cycle.

30

Those skilled in the art will readily note that these synthetic steps are sequence specific, that is they are specifically correlated to the desired synthesis. Herein, these synthesis steps are referred 35 to as a "sequence specific timing protocol." In

considering to initiate a new synthesis, the "sequence specific timing protocol" of the new desired synthesis is compared to the sequence specific steps or timing protocol for those sequences already initiated. These 5 latter sequence specific steps are referred to as a "cumulative remaining timing protocol" because they are a compilation of all the individual "sequence specific timing protocols" of currently initiated syntheses.

10

More particularly, the above comparison requires the system to plot out when the active synthetic steps of the new desired synthesis occur with respect to the active synthetic steps of the sequences currently 15 being synthesized. And, unless there is a timing conflict in performing the active synthetic steps of the new desired synthesis and those already initiated, the system begins to initiate the start of the new synthesis, if necessary reagents are available. It 20 should be understood that the new sequence specific timing protocol of the desired new synthesis is added to the "cumulative remaining timing protocol."

Should, however, a timing conflict exist, the 25 system attempts to determine if the initiation of the new desired synthesis can be delayed or "time shifted", up and until the start of the next active synthetic step of any of the initiated syntheses, so as to eliminate the timing conflict. Unless the 30 system is able to resolve the timing conflict, the system will not initiate the new desired synthesis, but will instead proceed to execute the next required active synthetic step of the syntheses currently in progress. Once the active synthetic step has been 35 performed, the system updates the "cumulative

remaining timing protocol" and then attempts again to resolve the timing conflict during the next passive synthetic step of any of the ongoing syntheses. This timing protocol is repeatably performed until all the 5 desired syntheses have been initiated.

Below is an illustrative description of the synthetic steps for the simultaneous synthesis of multiple peptides in accordance with the principles of 10 the timing protocol discussed above. It should be recalled that each synthetic protocol in the multiple synthesis is a sequenced cycle order of pre-programmed steps or procedures. For this illustrative description, one synthetic cycle consists of the 15 following synthetic steps: (i) washing the resin three times with dimethylformamide (DMF) for thirty (30) seconds each time; (ii) deprotecting the amino acid with fifty percent (50%) solution of piperidine/DMF for ten (10) minutes; (iii) washing the resin five (5) 20 times with dimethylformamide (DMF) for thirty (30) seconds each time; and (iv) two (2) hour coupling using three (3) molar excess of DIC/HOBt activated Fmoc protected amino acids.

25 After finishing the last synthetic cycle for each peptide, the synthesis is finished by washing, or by washing, deprotecting and washing, if that is applicable.

30 Robot system 30 operating in accordance with the above illustrative synthetic cycle positions a first resin syringe (peptide synthesis no. 1), manipulates the plunger to aspirate a wash solution of dimethylformamide (DMF), and then shakes the resin 35 syringe. This washes the resin with wash solution for

thirty (30) seconds. Preferably, the washing is repeated three times. Subsequently, the first resin syringe is used to aspirate from the delivery cup the deprotection reagents that have been dispensed by the 5 piston pump. This latter step is the "adding deprotection reagents" step. This repeated washing and adding deprotection reagents takes about five (5) minutes.

- 10 During deprotection, which lasts about ten (10) minutes, the synthesis system can advantageously direct the robot system to initiate washing and adding deprotection reagents for a second resin syringe or the next peptide synthesis (peptide synthesis no. 2).
- 15 Since that washing and adding deprotection reagents, however, only takes less than five minutes, there are at least five minutes still remaining before the deprotection is completed for the first resin syringe. To ensure that the respite time between steps is
- 20 minimized, the synthesis system further directs the robot system to initiate yet another washing and adding deprotection reagents for a third resin syringe (peptide synthesis no. 3).
- 25 Determining whether to initiate another washing and adding deprotection reagents for a subsequent resin syringe (the next peptide synthesis) is controlled automatically under program control by comparing the sequence specific timing protocol with
- 30 the cumulative remaining timing protocol, as discussed above. In effect, washing and adding deprotection agents are initiated if the least remaining time for deprotection is sufficiently long to complete the task.

Once deprotection has been completed for the first resin syringe, the synthesis system directs the robot system to position the first resin syringe so as to wash the resin for thirty seconds with 5 dimethylformamide (DMF). This is repeated, preferably, five times, after which the resin syringe is positioned in a temporary holding location. The amino acid syringe containing the desired amino acid to be coupled is next positioned and a preprogrammed 10 amount dispensed into the delivery cup which then receives a DIC solution. The first resin syringe is used to aspirate from the delivery cup the amino acid solution so as to couple that amino acid. This latter step is the "adding coupling reagents" step. 15 Likewise, the time for washing and adding coupling reagents takes about five (5) minutes. During that coupling, the synthesis system advantageously directs the robot system to initiate coupling for the second resin syringe (peptide synthesis no. 2), and then 20 subsequently for the third resin syringe (peptide synthesis no. 3).

Similarly, determining whether to initiate another washing and add coupling reagents for a 25 subsequent resin syringe or peptide synthesis is controlled automatically under program control by comparing the sequence specific timing protocol with the cumulative remaining timing protocol, as discussed above. In effect, washing and adding coupling 30 reagents are initiated if the least remaining time for coupling is sufficiently long to complete the task.

Once coupling has been initialized for all three resin syringes, that is the three peptide syntheses, 35 the synthesis system takes a fourth resin syringe

(peptide synthesis no. 4) and initiates washing and deprotection. The synthesis system initiates washing and deprotection for as many resin syringes (peptide syntheses) as possible before the least remaining 5 coupling time expires.

This procedure is repeated until the sequence of the shortest length peptide is assembled. If desired, an additional resin syringe can then be used to 10 synthesize a new peptide sequence.

The maximum amount of peptide synthesized is limited by the size of the syringe. For example, with 10 ml syringes containing about 500 mg of resin (0.5 15 mmol/g resin), it is anticipated that 0.25 mmol of peptide (ca 300 mg crude decapeptide) can be synthesized.

Those skilled in the art will readily note in the 20 above illustrative description that the coupling time for each peptide synthesis is the same - the earliest initiated coupling finishing prior to subsequently initiated couplings. In that situation, each new 25 initiated synthetic cycle for a peptide synthesis follows the order in which the prior cycle was initiated. Of course, it should be understood that different coupling times, if that is desired, may be used. The principles of the timing protocol, however, do not change - the system, if time permits, initiates 30 an active synthesis step of the next peptide synthesis during the passive steps of the prior peptide synthesis.

A program listing implementing the principles of the invention, including the timing protocol, is contained in the microfiche appendix.

5 Referring to Fig. 3, there is illustrated the timing protocol or timing relationship between washing, adding deprotection reagents, deprotection, adding coupling reagents and coupling for the multiple synthesis of twelve peptides using the above described
10 solid phase peptide synthetic protocol. Those skilled in the art will readily note based on the discussion above that during passive synthetic steps (deprotection and coupling), active synthetic steps in the synthetic cycles of the next peptide synthesis are
15 concurrently initiated with the prior peptide synthesis. For example, referring to Fig. 3, during deprotection of the first peptide synthesis (peptide synthesis no. 1), washing and adding deprotection reagents is initiated for the second and third peptide
20 syntheses (peptide synthesis nos. 2 and 3).

It should be understood that prior to initiating the synthesis of each compound, various parameter variables must be specified, in the synthetic protocol
25 of each desired peptide synthesis, including the kind and amount of solvent or reagents to be dispensed, and the length of time of the corresponding washing steps and/or reaction steps. Also, because aspiration is performed in adding deprotection reagents and adding
30 coupling reagents, the volume of air necessary to enable the efficient mixing of the resin and solvent must be specified.

In addition to the various parameter variables
35 which must be specified or retrieved from existing

stored synthetic protocols, the synthesis system must also be initialized with other information, including the assignment and identification of solvents and reagents contained in the peptide synthetic protocols;

5 the reagent and amino acid concentrations (mmol/ml) used to calculate the corresponding reagent and amino acid solution volumes, respectively; the size of the syringes; the amount of resin in the syringes; the substitution of resin in mmol/g; the positions and

10 content of each amino acid syringe, preferably identified by a three to five letter code, including its concentration and available volume; the peptide sequences desired to be synthesized using the identifying three to five letter codes; and for each

15 peptide its identifying code, and sequence. Preferably, the system prompts the user for the information. Alternatively, however, this information may be entered prior to initiating the peptide syntheses or stored in a file or database.

20

The order in which sequences to be synthesized are entered establishes their priority for synthesis, and establishes a synthesis queue. Advantageously, any compound can be entered with any priority. Also,

25 additional sequences can be added to the synthesis queue together with the necessary synthetic protocol. Also, additional reagents may be added, if necessary.

From the above information, the system calculates

30 whether the amount of amino acid and reagents is sufficient to prepare all the peptides. Unless there is enough amino acid and reagents available for the synthesis, the synthesis system will not initiate that synthesis, indicating instead its status as "not

35 ready." Significantly, the above timing protocol

allows handling multiple synthetic tasks efficiently since active synthetic steps requiring the use of the robot system in the synthesis cycles of multiple peptides are performed concurrently with passive 5 synthetic steps in different synthetic cycles. Moreover, because synthesis resources become immediately available with each completed synthesis, a new peptide synthesis can be initiated without waiting for the complete synthesis of the entire set of 10 desired peptides. Preferably, the new peptide synthesis is taken from the top of a waiting list of peptides that has been prioritized according to need. Advantageously, that prioritized waiting list can be changed at any time, either by adding or deleting any 15 peptide, to meet varying situations. Further, any peptide currently being synthesized can be halted without affecting the synthesis of the others.

Advantageously, since there is neither a physical 20 link between the reagent vessels and the reaction vessels nor between the mixing chambers and the reaction vessels, different reagents and reaction conditions may be used within the same or different peptide synthesis. Such flexibility, of course, 25 allows for the synthesis of libraries requiring variable numbers of building block reagents.

To test the reliability and throughput of the above novel peptide synthesis system, five different 30 peptide amides (IKRKR, VRYGI, AAAGY, FPRGR, VYFAW) were synthesized using a RAM TentaGel resin in accordance with the principles of the invention. Also, a mixture K (82.5% trifluoroacetic acid, 5% p- 35 cresol, 5% thioanisole, 2.5% ethanedithiol and 5% water) was used to deprotect side chains and to cleave

the peptides from the resin. Results from that experimental practice indicate, a high degree of purity of the crude material based on analytical gradient HPLC traces and molecular peak analysis using 5 mass spectroscopy.

It is understood that various other modifications will also be readily apparent to those skilled in the art without departing from the scope and spirit of the 10 invention. For example, the principles of the invention can be equally applied to any chemistry that involves repeated procedures, such as washing, deprotection and coupling - particularly, solid phase synthesis, including but not limited to the organic 15 reactions described in Borchardt et al., J. Am. Chem. Soc., 116: 373 (1994); Chen et al., J. Am. Chem. Soc., 116: 2661 (1994); Simon et al., PNAS, 89: 9367 (1992); Nikolaiev et al., Pept. Res., 6: 161-70 (1993); and 20 Lebl et al., Vol. 5: 541-548, Techniques In Protein Chemistry, Academic Press, San Diego (1994).

Accordingly, it is not intended that the scope of the claims appended hereto be limited to the description set forth herein, but rather that the 25 claims be construed as encompassing all the features of the patentable novelty that reside in the present invention, including all features that would be treated as equivalents thereof by those skilled in the art to which this invention pertains.

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Apparatus and Method for Multiple Synthesis of Organic Compounds on Polymer Support

Viktor Krchnak et al.

SUBSTITUTE SHEET (RULE 26)

Apparatus and Method for Multiple Synthesis of Organic Compounds on Polymer Support

Viktor Krchnak et al.

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```

; Procedure : AMINO
; Purpose   : Print the current values of amino acid volumes
; Author    : CES
;

disablekeys
filenew 2, "temp.prt"
if (num_codes)
  filewriteline 2, "Required Amino Acid Amounts"
  filewriteline 2, ""
  filewriteline 2, "Code Req. Avail Code Req. Avail Code Req. Avail Code
  filewriteline 2, ""
  a = 1
  while (a <= num_codes && a <= 50)
    a$ = ""
    stringformat b$, "#4.3s #5.1lf #5.1lf ", aalist_code$[a], aalist_req[a], aalist
    a$ = a$ + b$
    if (a+50 <= num_codes)
      stringformat b$, "#4.3s #5.1lf #5.1lf ", aalist_code$[a+50], aalist_req[a+50]
      a$ = a$ + b$
    endif
    if (a+100 <= num_codes)
      stringformat b$, "#4.3s #5.1lf #5.1lf ", aalist_code$[a+100], aalist_req[a+100]
      a$ = a$ + b$
    endif
    if (a+150 <= num_codes)
      stringformat b$, "#4.3s #5.1lf #5.1lf ", aalist_code$[a+150], aalist_req[a+150]
      a$ = a$ + b$
    endif
    filewriteline 2, a$
    a = a + 1
  endwhile
  filewriteline 2, ascii$(12)+"Available Amino Acid Amounts"
else
  filewriteline 2, "Available Amino Acid Amounts"
endif
filewriteline 2, ""
filewriteline 2, "          10 ml Syringe Rack           2.5 ml Syringe"
filewriteline 2, "Pos Code Conc Vol Pos Code Conc Vol Pos Code Conc Vol Po
a = 1
while (a <= 50)
  a$ = ""
  stringformat b$, "#3.0lf #4.3s #4.1lf #4.1lf ", a, acid_code$[a], acid_conc[a], ac
  a$ = a$ + b$
  stringformat b$, "#3.0lf #4.3s #4.1lf #4.1lf ", a+50, acid_code$[a+50], acid_conc[a+50]
  a$ = a$ + b$
  stringformat b$, "#3.0lf #4.3s #4.1lf #4.1lf ", a, acid_code$[a+100], acid_conc[a+100]
  a$ = a$ + b$
  stringformat b$, "#3.0lf #4.3s #4.1lf #4.1lf ", a+50, acid_code$[a+150], acid_conc[a+150]
  filewriteline 2, a$
  a = a + 1
endwhile

```

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fileclose z
fileprint "temp.prt"
enablekeys

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```

; Procedure : AMINO
; Purpose   : Allow operator to change amino acids
; Author    : MJB,CES
;= _____
local a,b,a$,b$,lastcoderow,startindex,sel_row
disablakeys
; Set the colors of the volumes -- set the ones that have their required
; greater than their available to red.
setnumarray code_color{1},15,-1
a = 1
while (a <= num_codes)
  if (aalist_req[a] > aalist_avail[a])
    code_color[a] = 4
  endif
  a = a + 1
endwhile

; Start off by showing all codes
a = 1
while (a <= 100)
  code_index[a] = a
  code_index[a+100] = a
  a = a + 1
endwhile
code_row = 0
lastcoderow = 0
te_row = 0
ten_col = 0
num_ten = 100
two_row = 0
two_col = 0
num_two = 100

; Store temporary data so we can go back to it
savevars 1,"tmpamino.dat"
savevars 2,"tmpcodes.dat"

screenon "amino"
enablekeys
user_choice = 0

while (user_choice != -1)
  if (user_choice == 1)
    call aminoprt.tcl
    user_choice = 0
  elseif (user_choice == 2)
    ; Clear all amino acid values
    ask user_choice,"Are you sure you want to clear\all amino data?"
    if (user_choice)
      setstringarray acid_code$[1], "",200
      setnumarray acid_conc[1],0,200
      setnumarray acid_avail[1],0,200

```

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```
calc_needed = 1
updateable
endif
user_choice = 0
elseif (user_choice == 5)
  ask user_choice,"Cancel changes to amino rack?"
  if (user choice)
    ; Retrieve temporary data
    loadvars 1,"tmpamino.dat"
    loadvars 2,"tmpcodes.dat"
    screenback
    stop
  endif
  user_choice = 0
elseif (code_row != lastcoderow)
  ; show a subset of the codes
  disablekeys
  screenhold
  if (code_row == 0)
    ; show all codes
    a = 1
    while (a <= 100)
      code_index[a] = a
      code_index[a+100] = a
      a = a + 1
    endwhile
    num_ten = 100
    num_two = 100
  else
    ; Only show the locations for the codes selected
    a$ = aalist_codes[code_row]
    ; Search through the 10 ml array and find ones that match
    num_ten = 0
    startindex = 0
    sarrayfind startindex,acid_codes[startindex+1],a$
    while (startindex != -1 && startindex <= 100)
      num_ten = num_ten + 1
      code_index[num_ten] = startindex
      sarrayfind startindex,acid_codes[startindex+1],a$
    endwhile
    ; Search through the 2.5 ml array and find ones that match
    num_two = 0
    startindex = 100
    sarrayfind startindex,acid_codes[startindex+1],a$
    while (startindex != -1)
      code_index[num_two+101] = startindex - 100
      num_two = num_two + 1
      sarrayfind startindex,acid_codes[startindex+1],a$
    endwhile
  endif
  lastcoderow = code_row
  updateable
  screenupdate
  enablekeys
elseif (ten_row || two_row)
```

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```

; Change amino acid
dissablekeys
; Figure out which amino acid rack
if (ten_row)
  sel_row = code_index(ten_row)
else
  sel_row = code_index[two_row + 100] + 100
endif
show sel_row
ten_row = 0
two_row = 0
if (fast_fill)
  ; automatically set the syringe to the full amount
  if (acid_code$(sel_row) != "")
    acid_avail[sel_row] = 2.5 + 7.5*(sel_row<=100)
  endif
else
  ; allow the user to set any of the values
  if (sel_row <= 100)
    b$ = "\n(10 ml rack, position " + numtostr$(sel_row) + ")"
  else
    b$ = "\n(2.5 ml rack, position " + numtostr$(sel_row-100) + ")"
  endif
  ; input the code: if changed, find the concentration from similar code
  a$ = acid_code$(sel_row)
  inputstring a$,"Enter the code:" + b$
  if (a$ != acid_code$(sel_row))
    acid_code$(sel_row) = a$
    sarrayfind startindex,acid_code$(1),a$
    if (startindex == sel_row)
      sarrayfind startindex,acid_code$(startindex+1),a$
    endif
    if (startindex != -1)
      acid_conc[sel_row] = acid_conc[startindex]
    else
      acid_conc[sel_row] = .1
    endif
    acid_avail[sel_row] = 0
  endif
  a = acid_conc[sel_row]
  inputnum a,"Enter the concentration:" + b$
  if (a != acid_conc[sel_row])
    startindex = 0
    sarrayfind startindex,acid_code$(startindex+1),a$
    while (startindex != -1)
      acid_conc[startindex] = a
      sarrayfind startindex,acid_code$(startindex+1),a$
    endwhile
  endif
  a = -1
  while (a < 0 || a > (2.5 + 7.5*(sel_row<=100)))
    a = acid_avail[sel_row]
    inputnum a,"Enter the available volume:" + b$
    if (a >= 0 && a <= (2.5 + 7.5*(sel_row<=100)))
      if (a != acid_avail[sel_row])

```

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```
    .cid_avail[sel_row] = a
  endif
else
  tellalarm "The volume must be between 0 and " + numtostr$(2.5 + 7.5*(s
endif
endwhile
endif
updatetable
screenupdate
enablekeys
endif
endwhile

savevars 1,"amino.dat"
savevars 2,"codes.dat"
screenback
```

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Procedure: BREAKSEQ
 Purpose : breaks sequence into individual codes
 Author : MJB
 Notes : Input - bs_seq\$
 Output - couplings = # of couplings
 code\$[couplings] = individual codes in sequence
 bs_error = 1 if error, 0 if valid sequence

```

local char$,seqlen,pos,a,b

seqlen = strlen(bs_seq$)
pos = 1
couplings = 0
bs_error = 0
setstringarray code$[1],"",-1

// Break sequence string into peptide codes
while (pos<=seqlen)
  char$ = mid$(bs_seq$,pos,1)
  if (isallalnum(char$))
    code$[couplings+1] = code$[couplings+1] + char$
  elseif (char$=="-")
    if (strlen(code$[couplings+1]))
      couplings = couplings + 1
  endif
  else
    bs_error = 1
    stop
  endif
  pos = pos + 1
endwhile
if (strlen(code$[couplings+1]))
  couplings = couplings + 1
endif

// Flip sequence around
a = 1

while (a<=couplings)
  flipcode$[a] = code$[a]
  a = a + 1
endwhile
  
```

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```
b = couplings
a = 1

while (a<=couplings)
  codeS[a] = flipcodeS[b]
  a = a + 1
  b = b - 1
endwhile
```

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```

; Procedure : CALC
; Purpose   : Calculate required and available volumes
; Author    : MJB,CES

local syringe,curamino,curprocess,cursequence$,curdodep$,mytime
timer mytime
disablekeys
sysmsg$ = "Waiting for robot..."
screenupdate
stringrequest "USING SYRINGES"

sysmsg$ = "Calculating required volumes..."
calc_needad = 0
screenupdate

num_codes = 0
setstringarray aalist_codes[0], "", -1
setnumarray aalist_req[0], 0, -1
setnumarray aalist_avail[0], 0, -1
setnumarray aalist_conc[0], 0, -1
setnumarray sol_req[1], 0, -1
syringe = 1
while (syringe <= num_syringes)

  sysmsg$ = "Calculating volumes (syringe " + numtostr$(syringe) + ")"
  screenupdate
  ; Only process the syringe if it has been assigned a location or it
  ; has already been started
  if (syr_loc[syringe] || syr_process(syringe) > 1)
    ; Set the process data to the syringe's current status or to the
    ; start if it hasn't begun
    if (syr_process(syringe) > 1)
      curprocess = syr_process(syringe)
      curamino = syr_amino_step(syringe)
    else
      curprocess = 2
      curamino = 1
    endif
    cursequence$ = syr_sequence$(syringe)
    curdodep$ = syr_dodeprot$(syringe)
    aa_short = 0
    buf_short = 0

    ; Find the amino acid code
    bc_seq$ = syr_sequence$(syringe)
    call breakseq.tcl

    ; Go through the protocol and figure out how much amino acid and
    ; reagent is required at each process step
    while ((prot_proc(curprocess) != step_finished) && (curprocess < num_procs))
      show "Step: " + prot_step$(prot_proc(curprocess))

```

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```

; Find amino volume required
aa_process = curprocess
aa_amino$ = code$(curamino)
aa_syringe = syringe
call calcaa.tcl

; Find solution and buffer volume
buf_process = curprocess
buf_syringe = syringe
call calcbuf.tcl

; Determine which step is next
stringrequest "NEXT STEP"
ns_process = curprocess
ns_amino = curamino
ns_dodep$ = curdodep$
call nextstep.tcl
curprocess = ns_process
curamino = ns_amino
stringfree "NEXT STEP"

endwhile

; Is there enough aa and buf for syringe to be processed?
if (aa_short || buf_short)
  calc_needed = 1
  if (syr_process(syringe) == 1)
    syr_process(syringe) = 0
  elseif (syr_process(syringe) > 1)
    tellalarm "Syringe #"+numtostr$(syringe)+" is in process\nbut will not h
  endif
  elseif (syr_process(syringe) == 0)
    syr_process(syringe) = 1
  endif
  endif
  syringe = syringe + 1
endwhile

sysmsg$ = ""
updatetable
screenupdate
enablekeys

show "calc took " + numtostr$(elapsed(mytime))
stringfree "USING SYRINGES"

```

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```

Procedure :: CALCAA
Purpose  : Calculate required amino acid for a step
Author   : MJB,CES
Notes    : Input: aa_process
           aa_amino$ 
           aa_syringe
           aa_short -- set if the avail is less than required

local c_index,rt_index,tempamount
if (prot_steps[prot_proc[aa_process]] == "Add Coupl.")
  ; Find the code in the "required" list, insert it if it isn't there
  sarrayfind c_index,aalist_code$[1],aa_amino$
  if (c_index == -1)
    num_codes = num_codes + 1
    aalist_code$[num_codes] = aa_amino$
    c_index = num_codes
  ; Now find the code in the RT racks and find the available volume
  sarrayfind rt_index,acid_code$[1],aa_amino$
  while (rt_index != -1)
    ; Find the total amount of amino acid
    aalist_avail[num_codes] = aalist_avail[num_codes] + acid_avail(rt_index)
    aalist_conc[num_codes] = acid_conc(rt_index)
    sarrayfind rt_index,acid_code$[rt_index+1],aa_amino$
  endwhile
  c_index = num_codes
  ; If
  ; determine the volume required
  if (aalist_conc[c_index])
    tempamount = syr_resin(aa_syringe) * syr_subst[aa_syringe] * prot_vol(aa_pro
    tempamount = tempamount / aalist_conc[c_index]
    aalist_req[c_index] = aalist_req[c_index] + tempamount
  else
    aalist_avail[c_index] = -1
    aalist_req[c_index] = 0
  endif
  if (aalist_req[c_index] > aalist_avail[c_index])
    aa_short = 1
  endif
endif

```

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```
;  
; Procedure : CALCBUF  
; Purpose   : Calculate the required buffer solutions  
; Author    : MJB,CES  
; Notes     : Input: buf_process  
;              buf_syringe  
;              buf_short -- set if avail is less than required  
;  
local temp$,sol_index  
  
temp$ = prot_step$(prot_proc(buf_process))  
if ("temp$ != "Add Coupl." && temp$ != "Wash" && temp$ != "Add Deprot.")  
  stop  
endif  
  
sarrayfind sol_index,contents$(1),prot_buf$(buf_process)  
if (sol_index == -1)  
  sysmsg$ = "Could not find buffer solution: "+prot_buf$(buf_process)  
  delay 1000  
  stop  
endif  
  
if (temp$ == "Wash")  
  sol_req(sol_index) = sol_req(sol_index) + prot_vol(buf_process)  
  sol_req(sol_index) = sol_req(sol_index) + cleaning_amount*3  
elseif (temp$ == "Add Coupl.")  
  sol_req(sol_index) = sol_req(sol_index) + (syr_resin(buf_syringe)*syr_subst(bu  
elseif (temp$ == "Add Deprot.")  
  sol_req(sol_index) = sol_req(sol_index) + prot_vol(buf_process)  
endif  
  
if (sol_req(sol_index) > sol_avail(sol_index))  
  buf_short = 1  
endif
```

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```
;  
; Procedure: CLEANCUP  
; Purpose  : clean coupling cup with solution  
; Author   : MJB  
;  
local b  
  
;find cleaning solution  
sarrayfind clean_buf1,prot_step$[1],"Wash"  
narrayfind clean_buf2,prot_proc(1),clean_buf1  
sarrayfind clean_buf,contents$[1],prot_buf$(clean_buf2)  
  
clean_cup_done = 1  
  
b = 0  
while (b<3)  
  ;dispense cleaning solution  
  if (!simulate_robot)  
    SYRINGE.dispense clean_buf,cleaning_amount  
  endif  
  delay 500  
  
  ;aspirate cleaning solution, fourth prob is vacuum probe  
  if (!simulate_robot)  
    SYRINGE.pipette 4,(cleaning_amount + .5)  
  endif  
  delay 500  
  
  b = b + 1  
end file  
  
SYRINGE.pipette 4,cleaning_amount  
clean_cup_done = 0
```

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```

; Procedure: CLEARALL
; Purpose: Clear all syringes from the system
; Author: CES
;-

local choice

sysmsg$ = ""
screenupdate
clear_all_syringes = 0
ask choice,"Are you sure you want to clear all syringes?"
if (!choice)
  enablekeys
  stop
endif

if (next_syringe > 1)
  ask choice,"Are you sure you want to clear all active syringes?"
  if (!choice)
    enablekeys
    stop
  else
    tell "Please remove ALL SYRINGES from the ROBOT SYSTEM now."
  endif

  sysmsg$ = "Clearing all syringes"

endif

scr_mupdate
; data for a sample
;setstringarray syr_pepcodes$[1],"",-1
;setstringarray syr_sequences$[1],"",-1
;setnumarray syr_size[1],10,-1
;setnumarray syr_rack[1],0,-1
;setnumarray syr_rackcc[1],0,-1
;setnumarray syr_loc[1],0,-1
;setnumarray syr_grip[1],0,-1
;setnumarray syr_amount[1],0,-1
;setnumarray syr_process[1],0,-1
;setnumarray syr_amino_step[1],0,-1      ;holds current coupling solution
;setnumarray syr_amino_count[1],0,-1      ;holds current coupling solution
;setnumarray syr_resin[1],2,-1
;setnumarray syr_subst[1],45,-1
;setstringarray syr_dodeprot$[1],"N",-1
;setnumarray syr_processtime[1],0,-1
;setstringarray syr_datetimes$[1],"",-1
;setnumarray syr_statcolor[1],0,-1
syr_pepcodes$[1] = "Default"
num_syringes = 0
next_syringe = 1
current_row = 1
restart_index = 0

```

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```
; Set required amino to zero
num_codes = 0
setstringarray aalist_codes[1],"",200
setnumarray aalist_req[1],0,200
setnumarray aalist_avail[1],0,200
setnumarray aalist_conc[1],0,200

screenupdate
savevars 5,"syringes.dat"
savevars 2,"codes.dat"
sysmsg$ = ""
screenupdate
enablekeys
```

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```

; Procedure: CLEARALL
; Purpose: Clear all syringes from the system
; Author: CES
;= _____

local choice

sysmsg$ = ""
screenupdate
clear_all_syringes = 0
ask choice, "Are you sure you want to clear all syringes?"
if (!choice)
  enablekeys
  stop
endif

if (next_syringe > 1)
  ask choice, "Are you sure you want to clear all active syringes?"
  if (!choice)
    enablekeys
    stop
  else
    tell "Please remove ALL SYRINGES from the ROBOT SYSTEM now."
  endif

  sysmsg$ = "Clearing all syringes"
endif

scr .nupdate
; data for a sample
setstringarray syr_pepcode$[1], "", -1
setstringarray syr_sequences$[1], "", -1
setnumarray syr_size[1], 10, -1
setnumarray syr_rack[1], 0, -1
setnumarray syr_rackloc[1], 0, -1
setnumarray syr_loc[1], 0, -1
setnumarray syr_grip[1], 0, -1
setnumarray syr_amount[1], 0, -1
setnumarray syr_process[1], 0, -1
setnumarray syr_amino_step[1], 0, -1
setnumarray syr_amino_count[1], 0, -1      ;holds current coupling solution
setnumarray syr_resin[1], .2, -1            ;holds current coupling solution
setnumarray syr_subst[1], .45, -1
setstringarray syr_dodeprot$[1], "N", -1
setnumarray syr_processtime[1], 0, -1
setstringarray syr_datetimes$[1], "", -1
setnumarray syr_statcolor[1], 0, -1
syr_pepcode$[1] = "Default"
num_syringes = 0
next_syringe = 1
current_row = 1
restart_index = 0

```

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```
; Set required amino to zero
num_codes = 0
setstringarray aalist_codes[1], "", 200
setnumarray aalist_req[1], 0, 200
setnumarray aalist_avail[1], 0, 200
setnumarray aalist_conc[1], 0, 200

screenupdate
savevars 5, "syringes.dat"
savevars 2, "codes.dat"
sysmsg$ = ""
screenupdate
enablekeys
```

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```
;/ Procedure: CLRRACK
; Purpose  : places a zero in rack position
;           and current position in gripper
; Author   : MJB
;
;clear input rack
;if (syr_loc[current_index])
;  syr_loc[current_index] = 0
;endif

;set rack to gripper
;syr_rack[current_index] = 10

;clear rack location
;syr_rackloc[current_index] = 0

;save changed rack variables
;savevars 5,"syringes.dat"
```

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```

; Procedure: COUPLING
; Purpose  : robot actions for coupling
; Author   : MJB
;-- 

local b,buf_place,infoindex
infoindex = 1

;find buffer in reagent table
sarrayfind buf_place,contents$(1),prot_buf$(syr_process[current_index])

;put RX syringe in holding rack if RX syringe in gripper
if (syr_rack[current_index]==10)
  if (syr_size[current_index]==10)
    rack_type = 1
  else
    rack_type = 2
  endif
  nest = 1
  grip = syr_grip[current_index]
  call puthold.tcl
  call stopchek.tcl
endif

;get RT syringe and dispense amino acid
getting_rt = 1
show cp_amino$ 
sar  ;find a,acid_code$(1),cp_amino$ 
acid_needed = syr_resin[current_index]*syr_subst[current_index]*prot_vol[syr_pro
amino_disp = acid_needed
amino_found = 0
amino_place = 0
while (!amino_found)
  sarrayfind amino_place,acid_code$[(amino_place+1)],cp_amino$ 
  if (acid avail[(amino_place)])
    amino_found = 1
  endif
endwhile
while ((acid avail[amino_place]+.001)<acid_needed)  ;get as many amino syringes
  rack_location = amino_place
  if (amino_place>100)
    rack_location = rack_location - 100
    rack_type = 4
  else
    rack_type = 3
  endif
  call getrack.tcl
  call stopchek.tcl
  grip = 1
  if (amino_place>100)
    syringe = 2
  else
    syringe = 1

```

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```

        endif
        nest = 2
        call puthold.tcl
        call stopchek.tcl
        grip = 2
        nest = 2
        call gethold.tcl
        call stopchek.tcl
        cup = 1
        restart_info$[infoindex] = "Add Coup: Began Dispensing " + numtostr$(dsp_amou
        savevars 7,"restart.dat"
        infoindex = infoindex + 1
        dsp_amount = acid_avail[amino_place]
        call syr_dsp.tcl
        call stopchek.tcl
        restart_info$[infoindex] = "Add Coup: Finished Dispensing " + numtostr$(dsp_a
        savevars 7,"restart.dat"
        infoindex = infoindex + 1
        acid_needed = acid_needed - acid_avail[amino_place]
        acid_avail[amino_place] = 0
        savevars 1,"amino.dat"
        grip = 2
        nest = 2
        call puthold.tcl
        call stopchek.tcl
        grip = 1
        nest = 2
        call gethold.tcl
        call stopchek.tcl
        rack_location = amino_place
        if (amino_place>100)
            rack_location = rack_location - 100
        rack_type = 4
        else
            rack_type = 3
        endif
        call putrack.tcl
        call stopchek.tcl
        amino_found = 0
        while_(!amino_found)
            sarrayfind amino_place,acid_code$[(amino_place+1)],cp_amino$[1]
            if ((acid_avail[amino_place])||(amino_place==1))
                amino_found = 1
            endif
        endwhile
        andwhile
        rack_location = amino_place      ;do final RT syringe dispense
        if (amino_place>100)
            rack_location = rack_location - 100
            rack_type = 4
        else
            rack_type = 3
        endif
        call gettrack.tcl
        call stopchek.tcl

```

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```

grip = 1
if (amino_place>100)
  syringe = 2
else
  ' inge = 1
endif
nest = 2
call puthold.tcl
call stopchek.tcl
grip = 2
nest = 2
call gethold.tcl
first_pulses = motor_pulses
call stopchek.tcl
cup = 1
dsp_amount = acid_needed
restart_infos[infoindex] = "Add Coup: Began Dispensing " + numtostr5(dsp_amount)
savevars 7,"restart.dat"
infoindex = infoindex + 1
call syr_dsp.tcl
call stopchek.tcl
acid_avail[amino_place] = acid_avail[amino_place] - acid_needed
savevars 1,"amino.dat"
restart_infos[infoindex] = "Add Coup: Finished Dispensing " + numtostr5(dsp_amount)
savevars 7,"restart.dat"
infoindex = infoindex + 1
grip = 2
nest = 2
check_motor = 1
call puthold.tcl
check_motor = 0
call stopchek.tcl
second_pulses = motor_pulses

;check that fluid was dispensed from syringe
if (!simulate_robot)
  if ( ((first_pulses-5)<second_pulses) && (second_pulses<(first_pulses+5)) )
    error_code = 3
    call error.tcl
  endif
endif

grip = 1
nest = 2
call gethold.tcl

call stopchek.tcl
rack_location = amino_place
if (amino_place>100)
  rack_location = rack_location - 100
  rack_type = 4
else
  rack_type = 3
endif
call putrack.tcl

```

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```
call stopchek.tcl
getting_rt = 0

;dispense buffer solution
restart_info$[infoindex] = "Add Coup: Began Dispensing Buffer"
savevars 7,"restart.dat"
infoindex = infoindex + 1
cup = 1
sarrayfind a,contents$[1],prot_buf$[syr_process(current_index)]
disp_amount = syr_resin(current_index)*syr_subst[current_index]*prot_vol[syr_pro
reagent_disp = disp_amount
buf_number = a
buf_amount = disp_amount
run disp buf.tcl
sol_avail[a] = sol_avail[a] - disp_amount
savevars 4,"reagents.dat"
if (log_robot)
  logrobot$ = "dispense : " + numtostr$(disp_amount) + " nozzle: " + numtostr$(a
  call logrobot.tcl
  logrobot$ = "solution : " + prot_buf$[syr_process(current_index)]
  call logrobot.tcl
endif
restart_info$[infoindex] = "Add Coup: Finished Dispensing Buffer"
savevars 7,"restart.dat"
infoindex = infoindex + 1

;get RX syringe from holding rack
if (syr_size[current_index]==10)
  syringe = 1
else
  syringe = 2
endif
grip = 2
nest = 1
call gethold.tcl
syr_grip[current_index] = 2
call stopchek.tcl

;squeeze out solution in syringe
if ((syr_size[current_index]==10&&syr_amount[current_index]>drop_amount1)|| (syr_
  call waste.tcl
  call stopchek.tcl
endif
restart_info$[infoindex] = "Add Coup: Emptied syringe"
savevars 7,"restart.dat"
infoindex = infoindex + 1

;aspirate solution in cup
restart_info$[infoindex] = "Add Coup: Began Aspirating Solution"
savevars 7,"restart.dat"
infoindex = infoindex + 1
asp_amount = disp_amount + amino_disp
air_amount = prot_air(syr_process(current_index))
call syr_asp.tcl
call stopchek.tcl
```

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```
restart_infos[infoindex] = "Add Coup: Finished Aspirating Solution"
savevars 7, "restart.dat"
infoindex = infoindex + 1

;c n cup
if (!simulate_robot)
  run cleanup.tcl
endif
```

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```
Procedure: DATRACK
Purpose  : places a gripper value in rack position
Author   : MJB
;-
;set syringe rack for current index
syr_rack(current_index) = rack_type

;clear rack location
syr_rackloc(current_index) = rack_location

;save changed rack variables
savevars 5,"syringes.dat"
```

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```

; Procedure: DELETE
; Purpose: Delete a syringe from the system
; Author: CES
;-- 

local choice,temp,a$,size$ 

if (prot_proc(syr_process(delete_row)) != step_finished && current_index == dele
    tellalarm "You must wait until the syringe is in the tumbler!"
    stop
endif

if (syr_process(delete_row) > 1 && prot_proc(syr_process(delete_row)) != step_fi
    ask choice,"The peptide is in progress.\nAre you sure you want to delete pepti
    if (!choice)
        stop
    endif
    sysmsg$ = "Waiting for robot..."
    screenupdate
    stringrequest "USING SYRINGES"
    syr_process(delete_row) = num_procs
    syr_processtime(delete_row) = time_now
    sysmsg$ = ""
    screenupdate
    tell "The peptide has been marked as finished.\nThe robot will eventually take
    stringfree "USING SYRINGES"
else
    if (user_choice == 3)
        if (prot_proc(syr_process(delete_row)) == step_finished)
            tell "The robot will remove this syringe automatically.\nPlease allow ROBO
            stop
        else
            ask choice,"Are you sure you want to delete peptide, " + syr_pepcodes$[dele
            endif
            if (!choice)
                stop
            else
                size$ = "from " + numtostr$(syr_size(delete_row)) + "ml INPUT RACK locatio
                tell "Please physically REMOVE this syringe\n" + size$ + numtostr$(syr_loc
            endif
    endif

; Write the information to the complete.dat file
if (prot_proc(syr_process(delete_row)) == step_finished)
    stringrequest "SYRFILE"
    fileopen 6,"complete.dat"
    sf row = delete_row
    call syrfile.tcl
    fileclose 6
    stringfree "SYRFILE"
endif

```

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```
sysmsg$ = "Deleting from list..."  
temp = delete row  
while (temp <= num_syringes)  
    syr_pepcodes$[temp] = syr_pepcodes$[temp+1]  
    syr_size[temp] = syr_size[temp+1]  
    syr_loc[temp] = syr_loc[temp+1]  
    syr_sequence$[temp] = syr_sequence$[temp+1]  
    syr_process[temp] = syr_process[temp+1]  
    syr_amino_step[temp] = syr_amino_step[temp+1]  
    syr_amino_count[temp] = syr_amino_count[temp+1]  
    syr_resin[temp] = syr_resin[temp+1]  
    syr_subst[temp] = syr_subst[temp+1]  
    syr_dodeprot$[temp] = syr_dodeprot$[temp+1]  
    syr_processtime[temp] = syr_processtime[temp+1]  
    syr_datetime$[temp] = syr_datetime$[temp+1]  
    syr_statcolor[temp] = syr_statcolor[temp+1]  
    syr_amount[temp] = syr_amount[temp+1]  
    syr_grip[temp] = syr_grip[temp+1]  
    syr_rack[temp] = syr_rack[temp+1]  
    syr_rackloc[temp] = syr_rackloc[temp+1]  
    temp = temp + 1  
endwhile  
num_syringes = num_syringes - 1  
if (next_syringe > delete row)  
    next_syringe = next_syringe - 1  
endif  
endif  
sysmsg$ = "Saving data to file..."  
screenupdate  
if (num_syringes == 0)  
    ; Set required amino to zero  
    num_codes = 0  
    setstringarray aalist_codes$[1], "", 200  
    setnumarray aalist_req[1], 0, 200  
    setnumarray aalist_avail[1], 0, 200  
    setnumarray aalist_conc[1], 0, 200  
    savevars 2, "codes.dat"  
endif  
savevars 5, "syringes.dat"  
sysmsg$ = ""  
screenupdate
```

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```
Procedure: DEPROTCT
Purpose  : robot actions for a deprotection
Author   : MJB

local buf_place,infoindex
infoindex = 1

;find buffer in reagent table
sarrayfind buf_place,contents$[1],prot_bufs[syr_process[current_index]]

;change to stroke grip
if (syr_grip[current_index]==1||(syr_rack[current_index]==6||syr_rack[current_index]==10))
  syringe = 1
else
  syringe = 2
endif
grip = 1
nest = 1
if (syr_grip[current_index]==1)
  call puthold.tcl
  call stopchek.tcl
endif
if (syr_size[current_index]==10)
  syringe = 1
else
  syringe = 2
  if
  grip = 2
  nest = 1
  call gethold.tcl
  syr_grip[current_index] = 2
  call stopchak.tcl
endif

;squeeze out solution in syringe
if ((syr_size[current_index]==10&&syr_amount[current_index]>drop_amount)|| (syr_size[current_index]==1&&syr_amount[current_index]<drop_amount))
  call waste.tcl
  call stopchek.tcl
endif

restart_info$[infoindex] = "Add Deprot: Emptied syringe"
savevars 7,"restart.dat"
infoindex = infoindex + 1

;dispense buffer
restart_info$[infoindex] = "Add Deprot: Started dispensing buffer"
savevars 7,"restart.dat"
infoindex = infoindex + 1
buf_number = buf_place
buf_amount = prot_vol[syr_process[current_index]]
if 7<syringe==2)
```

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```
buf_amount = buf_amount/division_factor
endif
run disp_buf.tcl
sol_avail(buf_place) = sol_avail(buf_place) - buf_amount
savevars 1,"amino.dat"
if (log_robot)
  logrobotS = "dispense : " + numtostr$(buf_amount) + " nozzle: " + numtostr$(bu
  call logrobot.tcl
  logrobotS = "solution : " + prot_buf$(syr_process(current_index))
  call logrobot.tcl
endif
restart_info$(infoindex) = "Add Deprot: Finished dispensing buffer"
savevars 7,"restart.dat"
infoindex = infoindex + 1

; aspirate buffer
restart_info$(infoindex) = "Add Deprot: Started aspirating buffer"
savevars 7,"restart.dat"
infoindex = infoindex + 1
cup = 2
if (syr_size(current_index)==10)
  syringe = 1
else
  syringe = 2
endif
asp_amount = buf_amount
air_amount = prot_air(syr_process(current_index))
if (syringe==2)
  air_amount = air_amount/division_factor
endif
call syr_asp.tcl
call stopchek.tcl
restart_info$(infoindex) = "Add Deprot: Finished aspirating buffer"
savevars 7,"restart.dat"
infoindex = infoindex + 1

;rotate
rot_time = 60*prot_time(syr_process(current_index))
call rotate.tcl
call stopchek.tcl
```

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```

; Procedure: JOSTEP
; Purpose: Perform the next step for the syringe
; Author: CES
; Notes: current_index is the syringe to work on

local process

process = prot_proc(syr_process[current_index])

if (process == step_ready)
  syr_rack[current_index] = (2-(syr_size[current_index]-2.5)/7.5)
  syr_rackloc[current_index] = syr_loc[current_index]
  syr_loc[current_index] = 0
  syr_amino_step[current_index] = 1

  ; This should always be true if we got here
  if (current_index == next_syringe)
    next_syringe = next_syringe + 1
  else
    tellalarm "Logic error: next_syringe updated incorrectly"
  endif
  updatetable

elseif (process == step_wash)
  call washing.tcl
  logrobots = prot_steps[process]
  if (log_procedure)
    call logrobot.tcl
  endif
  if (dont_wait)
    time_now = time_now + prot_robottime[syr_process[current_index]]
  else
    time_now = elapsed(0)
  endif

elseif (process == step_adddeprot)
  call deprotect.tcl
  logrobots = prot_steps[process]
  if (log_procedure)
    call logrobot.tcl
  endif
  if (dont_wait)
    time_now = time_now + prot_robottime[syr_process[current_index]]
  else
    time_now = elapsed(0)
  endif

elseif (process == step_addcoupl)
  bs_seq$ = syr_sequences[current_index]
  call breakseq.tcl
  cp_amino$ = codas[syr_amino_step[current_index]]
  call coupling.tcl
  l~robot$ = "Add Coupling: " + codes[syr_amino_step[current_index]]

```

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```
if (log_procedure)
  call logrobot.tcl
endif
if (dont_wait)
  time_now = time_now + prot_rebottime(syr_process[current_index])
else
  time_now = elapsed(0)
endif

elseif (process == step_deprotection || process == step_coupling)
  if (syr_rack[current_Index] != 5 && syr_rack[current_Index] != 6)
    call put_tum.tcl
    logrobot$ = "Put Tumbler\n"
    if (log_procedure)
      call logrobot.tcl
    endif
    if (dont_wait)
      time_now = time_now + prot_rebottime(syr_process[current_index])
    else
      time_now = elapsed(0)
    endif
    syr_processtime[current_index] = time_now + 60*prot_time(syr_process[current_index])
    current_index = 0
  else
    call get_tum.tcl
    logrobot$ = "Get Tumbler, overtime -- "+numtostr$(time_now-syr_processtime[current_index])
    if (log_procedure)
      call logrobot.tcl
    endif
    if (dont_wait)
      time_now = time_now + prot_rebottime(syr_process[current_index])
    else
      time_now = elapsed(0)
    endif
  endif

elseif (process == step_finished)
;dump off syringe in waste basket
logrobot$ = prot_step$(process)
if (log_procedure)
  call logrobot.tcl
endif
call finish.tcl
;delete syringe from list
delete_row = current_index
stringfree "USING SYRINGES"
call delete.tcl
stringrequest "USING SYRINGES"
current_index = 0
endif
```

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```
;;
; Procedure: DUMP
; Purpose  : drop finished syringe in basket
; Author   : MJB
;=
```

```
if (log_robot)
  logrobot$ = "dump -- " + numtostr$(current_index)
  call logrobot.tcl
endif

if (simulate_robot)
  stop
endif

request "ROBOT"

ROBOT.speed sp_fast
ROBOT.move "drop"
ROBOT.speed sp_slow
ROBOT.jog_s 0,0,-drop_jog
ROBOT.finish

ROBOT.open
delay 1000

ROBOT.jog_s 0,0,drop_jog
ROBOT.speed sp_med
free
```

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```
_____  
; Procedure: EQUIPINIT  
; Purpose: Starting procedure for robot and Hamilton  
; Author: MJB  
; Notes:  
_____  
  
disablekeys  
initialization = 0  
sysinit_message$ = "Please Wait..."  
robot_ready = 0 ; set a bit for each question  
syringe_ready = 0  
screenon "SYSINIT"  
if (!simulate_robot)  
    call robhome.tcl  
else  
    robot_ready = 1  
endif  
if (!robot_ready)  
    tell "Initialization cancelled"  
    free  
    screenback  
    stop  
endif  
  
/* Prepare Syringe Pump */  
  
if (!simulate_robot)  
    call syrinits.tcl  
else  
    syringe_ready = 1  
endif  
if (!syringe_ready)  
    tell "Initialization cancelled"  
    free  
    screenback  
    stop  
endif  
  
/* Homing Motor */  
sysinit_message$ = "Homing Motor"  
if (!simulate_robot)  
    call homamtr.tcl  
    call safemtr.tcl  
endif  
  
sysinit_message$ = ""  
screenupdate  
tell "Initialization complete"  
initialization = 1  
screenback
```

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```
Procedure: FINISH
Purpose  : dumps off finished syringe
Author   : MJB

if (syr_rack[current_index] == 5 || syr_rack[current_index] == 6)
    call get_tum.tcl
endif

;if in gripper, check grip, change if necessary
if (syr_rack[current_index]==10)
    if (syr_grip[current_index]==2)
        nest = 1
        grip = 2
        if (syr_size[current_index]==10)
            syringe = 1
        else
            syringe = 2
        endif
        call puthold.tcl
        syr_rack[current_index] = 0
        call stopchek.tcl
        nest = 1
        grip = 1
        if (syr_size[current_index]==10)
            syringe = 1
        else
            syringe = 2
        endif
        -all gethold.tcl
        syr_grip[current_index] = 1
        syr_rack[current_index] = 10
        call stopchek.tcl
    endif

;if in holding rack, get with move grip
elseif (syr_rack[current_index]==8||syr_rack[current_index]==9)
    if (syr_size[current_index]==10)
        syringe = 1
    else
        syringe = 2
    endif
    grip = 1
    nest = 1
    call gathold.tcl
    syr_grip[current_index] = 1
    syr_rack[current_index] = 10
    call stopchek.tcl

;if in other rack, get with move grip
else
    if (syr_size[current_index]==10)
        syringe = 1
    else
```

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```
syringe = 2
endif
call getrack.tcl
syr_grip(current_index) = 1
syr_rack(current_index) = 10
call stopchek.tcl

endif
;go to dump
call dump.tcl
```

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```

; Procedure: GETHOLD
; Purpose: Get a syringe from the holding nest
; Author: MJB
; Notes:

;
; set syringe = 1 for 10ml , 2 for 2.5ml
;           grip   = 1 for move grip , 2 for stroke grip
;           nest   = 1 for nest 1, 2 for nest 2

if (syringe==1)
  rack_location = 1
  rack_type = 8
else
  rack_location = 1
  rack_type = 9
endif

local get_repeat
get_repeat = 0

if (log_robot)
  logrobot$ = "gethold -- syringe :" + numtostr(syringe) + " grip : " + numtost
  call logrobot.tcl
endif

if (simulate_robot)
  if (!getting_rt)
    call clrrack.tcl
  endif
  stop
endif

request "ROBOT"
syringe_present = 1

while ((!syringe_present)||(!get_repeat))
;
  if (get_repeat)
  call puthold.tcl
;
endif

ROBOT.open
delay 500

ROBOT.speed sp_fast

  if (grip!=2)
;
    ROBOT.move "mixsafe1"
;
  else

```

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```

;   ROBOT.move "mixsafe2"
;   run homamtr.tcl
;endif

a$ = "tmp" + numtostr$(syringe) + "_" + numtostr$(grip) + "_" + numtostr$(nest)
ROBOT.speed sp_mad

ROBOT.move a$
ROBOT.finish

if ((!syringe_present)&&(get_repeat))
  error_code = 1          /* CHANGE THIS CODE IF NECESSARY */
  call error.tcl
endif

ROBOT.speed sp_slow

if (grip==2)
  while (!home_done)
  .endwhile
endif

a$ = "tlw" + numtostr$(syringe) + "_" + numtostr$(grip) + "_" + numtostr$(nest)
if (grip==2)
  ROBOT.speed sp_mslow
endif

ROBOT.move_s a$
ROBOT.finish

if (grip==2)
  /* Routine to find the top of the syringe*/
  call findtop.tcl
  if (syringe==1)
    direction = 0
    motor_steps = syrg1_back
  endif
  if (syringe==2)
    direction = 0
    motor_steps = syrg2_back
  endif
  call strkmtr.tcl
  /*-----*/
endif

delay 1000
ROBOT.close
delay 500

if (grip==1)
  ROBOT.speed sp_slow

```

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```
else
    ROBOT.speed sp_vslow
endif

; a$ = "tmp" + numtostr$(syringe) + "_" + numtostr$(grip) + "_" + numtostr$(nest
ROBOT.move a$ a$ 
ROBOT.finish

; a$ = "mixsafe" + numtostr$(grip)
ROBOT.speed sp_med

; ROBOT.move a$ 

call syr_chk.tcl           ;find syringe
get_repeat = get_repeat + 1
endwhile

if (!getting_rt)
    syr_grip[current_index] = grip
    call clrrack.tcl
endif

free
```

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GETRACK
pick up bottle from any rack and return to safe position

USE OF PROCEDURE:

before calling this procedure set the variable:

rack_type = the type of rack
1 - 10ml RX
2 - 2.5ml RX
3 - 10ml RT
4 - 2.5ml RT
5 - 10ml TUM
6 - 2.5ml TUM
7 - probe

rack_location = the location in the rack

trip = 1

if (log_robot)
logrobots = "gettrack -- rack: " + numtostr\$(rack_type) + " loc: " + numtostr\$(
call logrobot.tcl
endif

if (simulate_robot)
if (!getting_rt)
...ll cirrack.tcl
endif
stop
endif

request "ROBOT"

ROBOT.speed sp_vfast

if (rack_type==5)
tum1_continue=0
while (!tum1_latched)
endwhile
elseif (rack_type==6)
tum2_continue=0
while (!tum2_latched)
endwhile
endif

ROBOT.open

found = 0
robot_i = 0
while (!found)
if (rack_location <= robot_i * row_size(rack_type))

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```

if ((rack_type==3) || (rack_type==4))
  ROBOT.move "rack_in"
endif

  rack_temps = rack_high$(rack_type) + numtostr$(robot_i)
  ROBOT.move rack_temp$
  ROBOT.finish
  found = 1
else
  robot_i = robot_i + 1
endif
endwhile

ROBOT.speed sp_fast

jog_temp = (track_jog[rack_type]*((row_size(rack_type)*robot_i) - rack_location)
ROBOT.joint 6,-jog_temp
ROBOT.finish

ROBOT.speed sp_slow
ROBOT.jog_s 0,0,-rack_jog[rack_type]
ROBOT.finish

delay 500
ROBOT.close
delay 500

ROBOT.speed sp_slow
ROBOT.jog_s 0,0,rack_jog[rack_type]
ROBOT.finish

if (rack_type!=7)
  ROBOT.speed sp_fast
  call syr_chk.tcl      ;find syringe
  while (!syringe_present)
    ROBOT.speed sp_med
    ROBOT.move "mixsafe1"
    ROBOT.move rack_temp$
    ROBOT.joint 6,-jog_temp
    error_code = 1        /* CHANGE THIS CODE IF NECESSARY */
    call error.tcl
    ROBOT.open
    delay 200
    ROBOT.finish
    ROBOT.speed sp_slow
    ROBOT.jog_s 0,0,-rack_jog[rack_type]
    ROBOT.finish
    ROBOT.close
    delay 200
    ROBOT.jog_s 0,0,rack_jog[rack_type]
    call syr_chk.tcl
  endwhile
endif

ROBOT.speed sp_fast

```

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```
if (!getting_rt)
    syr_grip(current_index) = 1
    call clrrack.tcl
end

if(rack_type==5)
    tum1_continue=1
elseif (rack_type==6)
    tum2_continue=1
endif

free
```

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```
;  
; Procedure: GET_TOM  
; Purpose: get syringe from tumbler  
; Author: MJB  
;  
rack_type = syr_rack[current_index]  
rack_location = syr_rackloc[current_index]  
  
call gettrack.tcl  
syr_grip[current_index] = 1  
call stopchek.tcl
```

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```
=====
; Procedure: HOMEMTR
; Purpose   : turn on motor until top sensor is triggered
; Author    : MJB
=====

home_done = 0

;turn on motor for backward direction

SHARK.writebit 224,0
delay 500
SHARK.writebit 404,1

SHARK.readbit i_sense_home,a
tester1 = 0

timer homemtr_time
while (!a)
  SHARK.readbit i_sense_home,a
  if (elapsed(homemtr_time)>30)

    ;stop motor from homing
    SHARK.writebit 404,0

    ;call error routine
    error_code = 4
    call error.tcl

    ;stroke motor down
    direction = 1
    motor_steps = 20
    call strkmtr.tcl

    ;start motor to home again
    SHARK.writebit 224,0
    delay 500
    SHARK.writebit 404,1
    timer homemtr_time

  endif
endwhile

home_done = 1
```

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```

; Procedure: INIT
; Purpose  : initialize system variables
; Author   : MJB
;=====

; Protocol procedure descriptions and parameter mask
param_buf = 1
param_vol = 2
param_air = 4
param_time = 8
param_condition = 16
param_robottime = 32
param_stop = 64
setstringarray prot_step${0}, "", -1
setnumarray prot_choice[0], 0, -1
step_notready = 0
step_ready = 1
step_wash = 2
step_adddeprot = 3
step_addcoupl = 4
step_deprotection = 5
step_coupling = 6
step_nextamino = 7
step_stopifnofinaldep = 8
step_finished = 9
prot_step${step_notready} = "Not Ready"
prot_step${step_ready} = "Ready"
prot_step${step_wash} = "Wash"
prot_choice[step_wash] = param_buf + param_vol + param_air +
param_time + param_robottime
prot_step${step_adddeprot} = "Add Deprot."
prot_choice[step_adddeprot] = param_buf + param_vol + param_air +
param_time + param_robottime
prot_step${step_addcoupl} = "Add Coupl."
prot_choice[step_addcoupl] = param_buf + param_vol + param_air +
param_robottime
prot_step${step_deprotection} = "Deprotection"
prot_choice[step_deprotection] = param_time + param_stop
prot_step${step_coupling} = "Coupling"
prot_choice[step_coupling] = param_time + param_stop
prot_step${step_nextamino} = "Next Amino"
prot_step${step_stopifnofinaldep} = "Stop If No Final Dep."
prot_choice[step_stopifnofinaldep] = param_condition
prot_step${step_finished} = "Finished"
prot_choice[step_finished] = param_stop

; Variables to keep track of syringes in system
num_syringes = 0      ; total number of syringes that have been input
next_syringe = 1       ; next syringe that will be removed from the
incoming rack
getting_rt = 0          ; flag to tell an RT syringe is in system
dont_do_next = 0        ; flag to tell max number of syringes in
system

```

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```

clear_all_syringes = 0 ; flag to tell robot procedure to clear all
syringes
setstringarray restart_info$[1], "", -1

; data for a sample
setstringarray syr_pePCODE$[1], "", -1
setstringarray syr_sequence$[1], "", -1
setnumarray syr_size[1], 10, -1
setnumarray syr_rack[1], 0, -1
setnumarray syr_rackloc[1], 0, -1
setnumarray syr_loc[1], 0, -1
setnumarray syr_grip[1], 0, -1
setnumarray syr_amount[1], 0, -1
setnumarray syr_process[1], 0, -1
setnumarray syr_amino_step[1], 0, -1           ;holds current coupling
solution
setnumarray syr_amino_count[1], 0, -1          ;holds current coupling
solution
setnumarray syr_resin[1], .2, -1
setnumarray syr_subst[1], .45, -1
setstringarray syr_dodeprot$[1], "N", -1
setnumarray syr_processtime[1], 0, -1
setnumarray syr_statcolor[1], 0, -1
setstringarray syr_datetime$[1], "", -1
syr_pePCODE$[1] = "Default"

;// Record structure for amino acids, set once then retrieve from
disk
setstringarray acid_code$[1], "", 200
setnumarray acid_conc[1], 0, 200
setnumarray acid_avail[1], 0, 200
fast_fill = 0

; Number of amino acids that appear in sequences
num_codes = 0

; Number of steps in current protocol
num_procs = 0

;Robot Speed Variables
sp_vslow = 5
sp_mslow = 20
sp_slow = 30
sp_mod = 50
sp_med = 70
sp_fast = 90
sp_vfast = 100

; Rack Variables
rack5_full = 0 ;set to keep track of whether or not tumblers are
full
rack6_full = 0
rt_get = 0      ;set to RT rack location when RT in system
rack_type = 1   ; 1 = 10ml RX syringe

```

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```

; 2 = 2.5ml RX syringe
; 3 = 10ml RT syringe
; 4 = 2.5ml RT syringe
; 5 = 10ml tumbler
; 6 = 2.5ml tumbler
; 7 = probe
; 8 = 10ml holding
; 9 = 2.5ml holding
; 10 = gripper

row_size[1] = 6
row_size[2] = 6
row_size[3] = 20
row_size[4] = 20
row_size[5] = 8
row_size[6] = 8
row_size[7] = 5
rack_jog[1] = 8
rack_jog[2] = 8
rack_jog[3] = 8
rack_jog[4] = 8
rack_jog[5] = 8
rack_jog[6] = 8
rack_jog[7] = 4
track_jog[1] = 1.5
track_jog[2] = 1.5
track_jog[3] = 1.5
track_jog[4] = 1.5
track_jog[5] = 1.5
track_jog[6] = 1.5
track_jog[7] = 2
rack_safe$[1] = "RXSAFE"
rack_safe$[2] = "RXSAFE"
rack_safe$[3] = "RTSAFE"
rack_safe$[4] = "RTSAFE"
rack_safe$[5] = "TUMSAFE"
rack_safe$[6] = "TUMSAFE"
rack_safe$[7] = "MIXSAFE1"
rack_high$[1] = "RX1"
rack_high$[2] = "RX2"
rack_high$[3] = "RT1"
rack_high$[4] = "RT2"
rack_high$[5] = "TUM1"
rack_high$[6] = "TUM2"
rack_high$[7] = "PRB"

; / Syringe Variables /
syringe = 1 ; 1 is 10ml syringe, 2 is 2.5ml syringe
temp_jog = 8

; / Cup Variables /
cup = 1 ; 1 for RGP1, 2 for RGP2
cup_jog = 4

; / Waste Variables /

```

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```

waste_jog = 3

; / Finished Peptide Basket Variables /
drop_jog = 8

; / Check Syringe Presence Variables /
syringe_sense_im$(1) = "IM_1"
syringe_sense_im$(2) = "IM_2"
syringe_sense_begin1$(1) = "CKB_11"
syringe_sense_begin1$(2) = "CKB_12"
syringe_sense_end1$(1) = "CKE_11"
syringe_sense_end1$(2) = "CKE_12"
syringe_sense_begin2$(1) = "CKB_21"
syringe_sense_begin2$(2) = "CKB_22"
syringe_sense_end2$(1) = "CKE_21"
syringe_sense_end2$(2) = "CKE_22"
syringe_sense_im$(3) = "IM_3"
syringe_sense_begin1$(3) = "CKB_13"
syringe_sense_end1$(3) = "CKE_13"
syringe_sense_begin2$(3) = "CKB_23"
syringe_sense_end2$(3) = "CKE_23"

; / Shark Inputs /

s = 24
a = 0

;while (s==24){!a)

    erroroff
    table_position = 1
    system_start = 0
    sense_table = 1
    sense_syringe = 2
    sense_press = 3
    sense_home = 4
    sensor_latch = 551
    motor_finish = 225
    sense_tum1 = 5
    sense_tum2 = 6
    SHARK.puttable
    table_position,system_start,sense_table,sense_syringe,sense_press,s
    ence_home,sensor_latch,motor_finish,sense_tum1,sense_tum2
    i_system_start = 1
    i_sense_table = 2
    i_sense_syringe = 3
    i_sense_press = 4
    i_sense_home = 5
    i_sensor_latch = 6
    i_motor_finish = 7
    i_sense_tum1 = 8
    i_sense_tum2 = 9
    SHARK.readbit i_system_start,a
    status s

```

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```

;counter inputs
pulses_counter = 2
putelapsed 10,pulses_counter
i_motor_pulses = 10

; if (s==24||!a)
; tell "Turn the Selector Switch to ON\nand pull out the
Emergency Stop button"
; endif
;endwhile

erroron

; / Shark Outputs /
o_tum1_start = 220
o_tum2_start = 221
o_tum1_clamp = 222
o_tum1_latch = 223
o_grip_dir = 224
o_grip_pulse = 225
o_buzzer = 226
o_syringe_locate = 227
o_tum2_clamp = 240
o_tum2_latch = 241
o_start_counter = 414
o_clear_counter = 415
o_clear_sensor = 550

; / Initialize Shark Outputs/
SHARK.writebit o_tum1_start,0 ;up
SHARK.writebit o_tum2_start,0 ;up
SHARK.writebit o_tum1_latch,0 ;open
SHARK.writebit o_tum2_latch,0 ;off
SHARK.writebit o_tum1_clamp,1 ;open
SHARK.writebit o_tum2_clamp,1 ;off
SHARK.writebit o_grip_dir,0 ;off
SHARK.writebit o_grip_pulse,0 ;open
SHARK.writebit o_buzzer,0 ;off

; / Error Variables /
error = 0
error_code = 0
err_syringe_sensor = 2
err_syringe_presence = 3

; / Error Messages /
error_message$[0] = ""
error_message$[100] = ""
error_message$[1] = "No Syringe Found"
error_message$[2] = "Syringe Sensor Not Reset"
error_message$[3] = "Syringe Did Not Dispense"
error_message$[4] = "Motor Did Not Home"
error_message$[5] = "Top of Syringe Not Found"
error_message$[101] = ""

```

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```
error_message$[102] = ""
error_message$[103] = ""
error_message$[104] = ""
error_message$[105] = ""

; / Error Solutions /
error_solution$[0] = ""
error_solution$[100] = ""
error_solution$[1] = "Place a Syringe in the Space"
error_solution$[101] = "Directly Below the Robot Gripper"
error_solution$[2] = "Check to Ensure PLC is on"
error_solution$[102] = ""
error_solution$[3] = "Manually Add Solution"
error_solution$[103] = "to RGP1"
error_solution$[4] = "The Motor will Try to Home"
error_solution$[104] = "When Error is Cleared"
error_solution$[5] = "The Motor will Try to Find Syringe"
error_solution$[105] = "Top When Error is Cleared"

; / Alarm Variables /
alarm_time = 1

initialization = 0      ; set to 1 when equipment initialized
current_index = 0
simulate = 0
syrg_done = 0
running = 0
rinsing_cup = 0          ;flag for washing cup in coupling
cleaning_amount = 10    ;amount of DMF to clean the cup with
sysmsg$ = ""

; / Data Input Variables /
prot_file$ = ""
reg_file$ = ""

;Simulate Variables
stop_blinking = 0
simulate_robot = 0
log_robot = 0
log_procedure = 0
dont_wait = 0

;Calibration data
motor_safe_step = 70
syrg1_cal_asp = 14.5
syrg2_cal_asp = 40
syrg1_cal_dsp = 14.5
syrg2_cal_dsp = 40
syrg1_back = 6
syrg2_back = 5
drop_amount1 = .5
drop_amount2 = .3
dsp_drop_amount1 = .2
dsp_drop_amount2 = .1
```

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```
unstick_amount1 = .5
unstick_amount2 = .1

;Create robot log file
filecloseall
filenew 1,"roblog.dat"
filecloseall

stringfree

robot_running = 0
shake_running = 0
check_motor = 0
clean_cup_done = 0

; load the current variables
call loadvars.tcl
```

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```

; Procedure: INSERT
; Purpose: Insert syringes into the system
; Author: CES
;

local choice,temp

; Determine the sequence(s) that will be inserted
numseq = 0
if (user_choice == 1)
    ; Ask the operator to input the Peptide's code and sequence
    numseq = 1
    tempcode$[1] = ""
    tempseq$[1] = ""
    inputstring tempcode$[1],"Enter the Peptide Code:"
    inputlongstring tempseq$[1],"Enter the sequence:"
    if (tempcode$[1] == "" || tempseq$[1] == "")
        numseq = 0
    endif
elseif (user_choice == 2)
    ; Get the sequence or group of sequences from a file
    call seqfile.tcl
endif

; Check whether there is enough room for insertion
if (numseq + num_syringes > 100)
    tellalarm "A maximum of " + numtostr$(100-num_syringes) + " syringes can be ad
end"

; Tell operator if insert action is cancelled
if (numseq == 0)
    tell "No syringe will be inserted"
    stop
endif

; Determine whether the Peptide codes and sequences are valid
sysmsg$ = "Checking for validity..."
screenupdate
temp = 1
while (temp <= numseq)
    if (strlen(tempcode$[temp]) > 8)
        sysmsg$ = ""
        screenupdate
        tellalarm "The code,\n" + tempcode$[temp] + ",\nis invalid."
        tell "No syringe will be inserted."
        stop
    endif
    bs_seq$ = tempseq$[temp]
    call breakseq.tcl
    if (bs_error)
        sysmsg$ = ""
        screenupdate
        tellalarm "The sequence,\n" + left$(tempseq$[temp],200) + ",\nis invalid."

```

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```
tell "... syringes will be inserted."
stop
endif
if ((!strlen(tempcode$(temp))) || (!couplings))
  sysmsg$ = ""
screenupdate
tellalarm "Codes and sequences cannot be empty."
tell "No syringe will be inserted."
stop
endif
syr_amino_count[temp] = couplings
tempcount[temp] = couplings
temp = temp + 1
endwhile

; Insert the sequences into the list of sequences
sysmsg$ = "Inserting into list..."
screenupdate
temp = num_syringes+numseq+1
while (temp >= current_row+numseq)
  syr_pepcodes[$temp] = syr_pepcodes[$temp-numseq]
  syr_size[$temp] = syr_size[$temp-numseq]
  syr_rack[$temp] = syr_rack[$temp-numseq]
  syr_loc[$temp] = syr_loc[$temp-numseq]
  syr_sequences[$temp] = syr_sequences[$temp-numseq]
  syr_process[$temp] = syr_process[$temp-numseq]
  syr_amino_step[$temp] = syr_amino_step[$temp-numseq]
  syr_amino_count[$temp] = syr_amino_count[$temp-numseq]
  syr_resin[$temp] = syr_resin[$temp-numseq]
  syr_subst[$temp] = syr_subst[$temp-numseq]
  syr_dodeprot[$temp] = syr_dodeprot[$temp-numseq]
  syr_processtime[$temp] = syr_processtime[$temp-numseq]
  syr_datetime[$temp] = syr_datetime[$temp-numseq]
  syr_statcolor[$temp] = syr_statcolor[$temp-numseq]
  temp = temp - 1
endwhile
temp = current_row
while (temp <= current_row+numseq-1)
  syr_pepcodes[$temp] = tempcode$[temp-current_row+1]
  syr_sequences[$temp] = tempseq$[temp-current_row+1]
  syr_amino_count[$temp] = tempcount[$temp-current_row+1]
  syr_size[$temp] = syr_size[$temp+num_syringes+numseq+1]
  syr_rack[$temp] = 0
  syr_loc[$temp] = 0
  syr_process[$temp] = 0
  syr_amino_step[$temp] = 1
  syr_resin[$temp] = syr_resin[$temp+num_syringes+numseq+1]
  syr_subst[$temp] = syr_subst[$temp+num_syringes+numseq+1]
  syr_dodeprot[$temp] = syr_dodeprot[$temp+num_syringes+numseq+1]
  syr_processtime[$temp] = 0
  syr_datetime[$temp] = date$() + " " + time$()
  syr_statcolor[$temp] = syr_statcolor[$temp+num_syringes+numseq+1]
  temp = temp + 1
endwhile
num_syringes = num_syringes + numseq
```

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symsg\$ = Saving data to file..."
screenupdate
savevars 5,"syringes.dat"
symsg\$ = ""
sc inupdate

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```
;  
;  
; Procedure: LOADVARS  
; Purpose  : Load system variables from disk and  
;             set other variables accordingly  
; Author   : MJB,CES  
;  
local a  
  
; Define Variable Groups for data storage  
  
;amino acid rack  
clearvargroup 1  
addvar 1,fast_fill,1  
addvar 1,acid_codeS[1],200  
addvar 1,acid_conc[1],200  
addvar 1,acid_avail[1],200  
  
; Amino acids that appear in sequences  
clearvargroup 2  
addvar 2,num_codes  
addvar 2,aalist_codeS[1],200  
addvar 2,aalist_req[1],200  
addvar 2,aalist_avail[1],200  
addvar 2,aalist_conc[1],200  
  
; current synthetic protocol  
clearvargroup 3  
addvar 3,num_procs  
addvar 3,prot_proc[1],200  
addvar 3,prot_bufS[1],200  
addvar 3,prot_vol[1],200  
addvar 3,prot_air[1],200  
addvar 3,prot_time[1],200  
addvar 3,prot_robottime[1],200  
  
; reagents and solutions  
clearvargroup 4  
addvar 4,contentsS[1],10  
addvar 4,sol_conc[1],10  
addvar 4,sol_req[1],10  
addvar 4,sol_avail[1],10  
  
;current syringe data  
clearvargroup 5  
addvar 5,num_syringes  
addvar 5,syr_papcodeS[1],100  
addvar 5,syr_sequencesS[1],100  
addvar 5,syr_size[1],100  
addvar 5,syr_rack[1],100  
addvar 5,syr_rackloc[1],100  
addvar 5,syr_loc[1],100  
addvar 5,syr_grip[1],100  
addvar 5,syr_amount[1],100  
addvar 5,syr_resin[1],100
```

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```

addvar 5,syr_subst[1],100
addvar 5,syr_dodeprot$[1],100
addvar 5,syr_process[1],100
addvar 5,syr_amino_step[1],100
addvar 5,syr_amino_count[1],100
addvar 5,syr_processtime[1],100
addvar 5,syr_datetime$[1],100

; Simulation flags
clearvargroup 6
addvar 6,simulate_robot
addvar 6,log_robot
addvar 6,log_procedure
addvar 6,dont_wait

; Current step state for restart purposes
clearvargroup 7
addvar 7,restart_info$[1],20

clearvargroup 8
addvar 8,division_factor

; Load variables from disk
erroroff
a = 0
loadvars 1,"amino.dat"
a = a + getstatus()
loadvars 2,"codes.dat"
a = a + getstatus()
loadvars 3,"lastprot.prt"
a = a + getstatus()
loadvars 4,"reagents.dat"
a = a + getstatus()
loadvars 5,"syringes.dat"
a = a + getstatus()
loadvars 6,"simulate.dat"
a = a + getstatus()
loadvars 7,"restart.dat"
a = a + getstatus()
loadvars 8,"division.dat"
a = a + getstatus()
erroron
if (a)
  ask a,"Some of the saved data did not load.\nDo you want to continue?"
  if (!a)
    terminate
  endif
endif

; Figure out the value for next_syringe
next_syringe = 1
while (next_syringe <= num_syringes && syr_process[next_syringe] > 1)
  next_syringe = next_syringe + 1
endwhile
syr_pcpcode$[num_syringes+1] = "Default"

```

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```
syr_sequence[num_syringes+1] = ""
syr_loc[num_syringes+1] = 0
syr_process[num_syringes+1] = 0

; ! 1 in the descriptions for the protocol steps
a = 1
while (a <= num_procs)
    prot_desc$(a) = prot_steps$(prot_proc(a))
    a = a + 1
endwhile
```

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```
;  
; Procedure: LOGROBOT  
; Purpose  : saves robot action and data  
; Author   : MJB  
;  
if (!dont_wait)  
    time_now = elapsed(0)  
endif  
  
fileopen 5,"roblog.dat"  
  
stringformat logrobot$, "t$ t03.0lf:t02.0lf:t02.0lf t-8s, ts", time$,(),(time_now-s  
fileappend 5,logrobot$  
fileclose 5
```

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```
;/ Procedure : PROTCHNG
;/ Purpose   : Allow operator to add, insert, or delete step
;/ Author    : MJB,CES
;-
; local temp
;
if (user_choice == 1)           ; add a procedure
  num_procs = num_procs + 1
  ; Set the selected row to be the added row
  prot_row = num_procs
  ; Set the column selection so that the user will be asked
  ; to input the type of procedure to add
  prot_col = 2
  prot_proc(prot_row) = 1
  prot_buf$(prot_row) = ""
  prot_vol(prot_row) = 0
  prot_air(prot_row) = 0
  prot_time(prot_row) = 0
  prot_robottime(prot_row) = 0
elseif (user_choice == 2)        ; insert a procedure
  screenhold
  num_procs = num_procs + 1
  temp = num_procs
  ; Move everything back in the protocol
  while (temp > prot_row)
    prot_proc(temp) = prot_proc(temp-1)
    prot_desc$(temp) = prot_desc$(temp-1)
    prot_buf$(temp) = prot_buf$(temp-1)
    prot_vol(temp) = prot_vol(temp-1)
    prot_air(temp) = prot_air(temp-1)
    prot_time(temp) = prot_time(temp-1)
    prot_robottime(temp) = prot_robottime(temp-1)
    temp = temp - 1
  endwhile
  ; Set the column selection so that the user will be asked
  ; to input the type of procedure to add
  prot_col = 2
  prot_proc(prot_row) = 1
  prot_buf$(prot_row) = ""
  prot_vol(prot_row) = 0
  prot_air(prot_row) = 0
  prot_time(prot_row) = 0
  prot_robottime(prot_row) = 0
elseif (user_choice == 3)        ; delete a procedure
  temp = prot_row
  if (temp < num_procs)
    ; Move everything forward in the protocol
    while (temp < num_procs)
      prot_proc(temp) = prot_proc(temp+1)
      prot_buf$(temp) = prot_buf$(temp+1)
      prot_vol(temp) = prot_vol(temp+1)
      prot_air(temp) = prot_air(temp+1)
      prot_time(temp) = prot_time(temp+1)
```

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```
~prot_robottime(temp) = prot_robottime(temp+1,
~temp = temp + 1
andwhile
else
; The selected row cannot be the deleted row
prot_row = prot_row - 1
endif
num_procs = num_procs-1
endif
```

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```

;----- Procedure : PROTCLIK
;----- Purpose   : Handle clicking on a column
;----- Author    : MJB,CES
;----- local a,a$,choice

; Allow the user to enter the data for a cell
if (prot_col==2)      ; change the procedure
  menuarray choice,prot_steps[1],"Pick a procedure:"
  if (choice != prot_proc[prot_row] && choice>0)
    prot_proc[prot_row] = choice
    prot_buf$[prot_row] = ""
    prot_vol[prot_row] = 0
    prot_air[prot_row] = 0
    prot_time[prot_row] = 0
    prot_robottime[prot_row] = 0
    prot_changed = 1
  endif
elseif (prot_col==3)   ; enter the buffer solution name
  if (prot_choice[prot_proc[prot_row]] & param_buf)
    a$ = prot_buf$[prot_row]
    inputstring a$,"Input Buffer Name"
    if (a$ != prot_buf$[prot_row])
      prot_buf$[prot_row] = a$
      prot_changed = 1
    endif
  endif
elseif (prot_col==4)   ; enter the buffer volume
  if (prot_choice[prot_proc[prot_row]] & param_vol)
    a = prot_vol[prot_row]
    inputnum a,"Input Volume of Buffer or Excess"
    if (a != prot_vol[prot_row])
      prot_vol[prot_row] = a
      prot_changed = 1
    endif
  endif
elseif (prot_col==5)   ; enter the air volume
  if (prot_choice[prot_proc[prot_row]] & param_air)
    a = prot_air[prot_row]
    inputnum a,"Input Volume of Air"
    if (a != prot_air[prot_row])
      prot_air[prot_row] = a
      prot_changed = 1
    endif
  endif
elseif (prot_col==6)   ; enter the time
  if (prot_choice[prot_proc[prot_row]] & param_time)
    a = prot_time[prot_row]
    inputnum a,"Input Time (min)"
    if (a != prot_time[prot_row])
      prot_time[prot_row] = a
      prot_changed = 1
    endif
  endif

```

```
        endif
    elseif (prot_col==7)      ; enter the robot use time.
        if (prot_choice(prot_proc[prot_row]) & param_robottime)
            a = prot_robottime[prot_row]
            inputint a, "Input the 'robot in use' time (sec):"
            if (a != prot_robottime[prot_row])
                prot_robottime[prot_row] = a
                prot_changed = 1
            endif
        endif
    endif
```

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```

; Procedure : PROTLD SV
; Purpose   : Load or save a protocol
; Author    : MJB,CES
;-- 

local choice,tempchanged

; Make sure there is a valid reagent specified for each step that needs one
choice = 1
while (choice <= num_procs)
  if (prot_choice[prot_proc[choice]] & param_buf)
    if (rtfim$(ltrim$(prot_buf$(choice))) == "")
      tell "You must input a buffer type for each step that needs one."
      prot_row = choice
      user_choice = 0
      stop
    endif
  endif
  choice = choice + 1
andwhile

; Make sure that the protocol starts with Ready and ends with Finished
if (prot_proc[1] != step_ready || prot_proc[num_procs] != step_finished)
  tellalarm "The protocol must begin with a 'Ready' step\nand end with a 'Finish'
  user_choice = 0
  stop
endif

; If the user is trying to quit or load, check if it needs saving
if (.ser_choice == 5 || user_choice == 6)
  if (prot_changed)
    ask prot_changed,"Do you want to save your changes\ninto a file?"
  endif
endif

if (prot_changed || user_choice == 4)
  // Save Protocol to Disk
  inputstring prot_file$, "Save Protocol As:\n(Do NOT add the Extension)"
  if (prot_file$ == "")
    user_choice = 0
    stop
  endif
  prot_file$ = prot_file$ + ".prt"
  filetest choice,prot_file$
  if (choice)
    ask choice,"That file exists.\nOverwrite?"
    if (!choice)
      user_choice = 0
      stop
    endif
  endiff
  erroroff
  savevars 3,prot_file$
  i" (getstatus())

```

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```
tellalarm "Error saving file.\n"+prot files
user_choice = 0
erroron
stop
endif
erroron
prot_changed = 0
endif

if (user_choice == 5)
// Retrieve Protocol from Disk
filetest choice,"*.prt"
if (choice>0)
filelist "*.prt",files$[1]
menuarray choice,files$[1],"Pick a File to Load:"
if (choice!=0)
savevars 3,"lastprot.prt"
erroroff
loadvars 3,files$[choice]
status choice
if (choice)
loadvars 3,"lastprot.prt"
tellalarm "That was an invalid protocol file.\nThe last protocol was re
prot_changed = 1
else
savevars 3,"lastprot.prt"
prot_changed = 0
endif
erroron
endif
else
prot_changed = 1
tell "No protocol files exist."
endif
endif

if (user_choice == 6)
user_choice = -1
else
user_choice = 0
endif
```

TESTIO.TCL

```
disablekeys

; initialize variables
num_puts = 7
si_nameS[1] = "System Start"
si_nameS[2] = "Table Sensor"
si_nameS[3] = "Top of Syringe"
si_nameS[4] = "Low Air"
si_nameS[5] = "Motor Home"
si_nameS[6] = "Tumbler #1 in Position"
si_nameS[7] = "Tumbler #2 in Position"
si_nameS[8] = ""
si_nameS[9] = ""
si_nameS[10] = ""
si_nameS[11] = ""
si_nameS[12] = ""
si_nameS[13] = ""
si_nameS[14] = ""
si_nameS[15] = ""
si_nameS[16] = ""
si_nameS[17] = ""
si_nameS[18] = ""
si_nameS[19] = ""
si_nameS[20] = ""

; change this line to reflect the addresses of the inputs
; keep the first parameter at one
SHARK.puttable 101,0,1,2,3,4,5,6

num_puts = 8
so_nameS[1] = "Tumbler Motor #1"
so_nameS[2] = "Tumbler Rack Locator #1"
so_nameS[3] = "Tumbler Syringe Clamp #1"
so_nameS[4] = "Tumbler Motor #2"
so_nameS[5] = "Tumbler Rack Locator #2"
so_nameS[6] = "Tumbler Syringe Clamp #2"
so_nameS[7] = "2.5ml Syringe Locator"
so_nameS[8] = "Buzzer"
so_nameS[9] = ""
so_nameS[10] = ""
so_nameS[11] = ""
so_nameS[12] = ""
so_nameS[13] = ""
so_nameS[14] = ""
so_nameS[15] = ""
so_nameS[16] = ""
so_nameS[17] = ""
so_nameS[18] = ""
so_nameS[19] = ""
so_nameS[20] = ""
so_address[1] = 220
so_address[2] = 223
so_address[3] = 222
so_address[4] = 221
```

```

so_address(0) = 241
so_address(6) = 240
so_address(7) = 227
so_address(8) = 226
so_address(9) = -1
so_address(10) = -1
so_address(11) = -1
so_address(12) = -1
so_address(13) = -1
so_address(14) = -1
so_address(15) = -1
so_address(16) = -1
so_address(17) = -1
so_address(18) = -1
so_address(19) = -1
so_address(20) = -1

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a = 1
while (a <= numoutputs)
  readbit so_address[a],so_on[a]
  a = a + 1
endwhile

stopme = 0
screenison = 0
doterminal = 0
terminal_running = 0
choice = 0
while (!stopme)

  if (choice)
    writebit so_address[choice],!so_on[choice]
    so_on[choice] = !so_on[choice]
    choice = 0
  endif

  a = 1
  while (a <= numinputs-10)
    readbit a+100,si_on[a],si_on[a+1],si_on[a+2],si_on[a+3],si_on[a+4],si_on[a+5]
    a = a + 10
  endwhile
  while (a <= numinputs-5)
    readbit a+100,si_on[a],si_on[a+1],si_on[a+2],si_on[a+3],si_on[a+4]
    a = a + 5
  endwhile
  while (a <= numinputs)
    readbit a+100,si_on[a]
    a = a + 1
  endwhile

  if (doterminal)
    if (!terminal_running)
      run terminal.tcl
    endif
  doterminal = 0

```

```
endif  
if (!screenison)  
  screenon "testio"  
  enablekeys  
  screenison = 1  
endif  
andwhile  
request "robot"  
ROBOT.command "NOMANUAL"  
free  
screenback
```

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-7/-

```
;/ Procedure : PROTOCOL
;/ Purpose  : Allow operator to change protocol data
;/ Author   : MJB,CES
;--  
  
local choice,simulate_change,temp  
  
simulate_change = simulate_robot+(dont_wait*2)+(log_robot*4)+(log_procedure*8)  
prot_col = 0  
prot_row = 0  
prot_changed = 0  
prot_file$ = ""  
prot_proc[0] = 0  
prot_proc[100] = 100  
screenon "protocol"  
  
user_choice = 0  
while (user_choice != -1)  
  
// Clicked on Synthetic Protocol Box  
if (prot_col)  
    screenupdate  
    if (next_syringe <= 1)  
        call protclik.tcl  
    endif  
    updatetable  
    screenupdate  
    prot_col = 0  
e' 'if'(user_choice == 7)  
    Change division factor  
    temp = division factor  
    inputnum temp,"Enter the new division factor:"  
    if (temp > 0 && temp <= 99.99)  
        division_factor = temp  
        savevars 8,"division.dat"  
        screenupdate  
    endif  
    user_choice = 0  
elseif ((user_choice && next_syringe <= 1) || user_choice == 6)  
    if (user_choice >= 1 && user_choice <= 3)  
        call protchnq.tcl  
    updatetable  
    screenupdate  
    user_choice = 0  
elseif (user_choice >= 4 && user_choice <= 6)  
    call protldsv.tcl  
    updatetable  
    screenupdate  
    endif  
endif  
endif  
  
endwhile  
  
;Save protocol to permanent file
```

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```
savevars 3,"lastprot.prt"
user_choice = 0
if (simulate_change=simulate_robot+(dont_wait*2)+(log_robot*4)+(log_procedure*8
    savevars 6,"simulate.dat"
    initialization = 0
endif

; Fill in the descriptions for the protocol steps
a = 0
while (a <= num_procs)
    prot_desc$[a] = prot_step$(prot_proc[a])
    a = a + 1
endwhile

screenback
```

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```
; Procedure: PUTHOLD
; Purpose: put a syringe in the holding rack
; Author: MJB
; Notes:
;
; set syringe = 1 for 10ml , 2 for 2.5ml
; grip   = 1 for move grip , 2 for stroke grip
; nest   = 1 for nest 1, 2 for nest 2
;
local a

if (syringe==1)
  rack_location = 1
  rack_type = 8
else
  rack_location = 1
  rack_type = 9
endif

if (log_robot)
  logrobots = "puthold -- syringe : " + numtostr$(syringe) + " grip : " + numtos
endif

if (simulate_robot)
  if ('!getting_rt')
    _all datrack.tcl
  endif
  stop
endif

request "ROBOT"

ROBOT.speed sp_fast
;a$ = "mixsafe"+ numtostr$(grip)
;ROBOT.move a$
ROBOT.speed sp_mod

a$ = "tmp" + numtostr$(syringe) + "_" + numtostr$(grip) + "_" + numtostr$(nest)
ROBOT.move a$

if (grip==1)
  ROBOT.speed sp_slow
else
  ROBOT.speed sp_vslow
endif
```

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```

a$ = "tlv" + numtostr$(syringe) + "_" + numtostr$(grip) + "_" + numtostr$(nest)
ROBOT.move_s a$
ROBOT.finish

ROBOT.open
if (grip==1&&syringe==2)
  delay 500
else
  delay 250
endif

if (grip==1)
  ROBOT.speed sp_med
else
  ROBOT.speed sp_slow
endif

if (grip==2)
  run homemtr.tcl
endif

;check motor pulses
if (grip==2&&check_motor)
  while (!home_done)
    endwhile
    call findtop.tcl
    run homemtr.tcl
  endif

a$ = "tmp" + numtostr$(syringe) + "_" + numtostr$(grip) + "_" + numtostr$(nest)
ROBOT.move_s a$

ROBOT.finish

if (syringe==2)
  SHARK.writebit o_syringe_locate,1
  delay 1500
  SHARK.writebit o_syringe_locate,0
endif

delay 500

if (grip==1&&syringe==2)
  ROBOT.speed sp_mslow

a$ = "tlv" + numtostr$(syringe) + "_" + numtostr$(grip) + "_" + numtostr$(nest)
ROBOT.move_s a$

ROBOT.finish

ROBOT.jog_s 0,0,.25
ROBOT.finish

ROBOT.close

```

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```
delay 250
ROBOT.open
delay 250
a$ = "tmp" + numtostr$(syringe) + "_" + numtostr$(grip) + "_" + numtostr$(nest)
ROBOT.move_s a$
ROBOT.finish
endif
a$ = "mixsafe" + numtostr$(grip)
;ROBOT.speed sp_fast
;ROBOT.move a$
if (grip==2)
  while (!home_done)
  andwhile
  run safemtr.tcl
endif
if (!getting_rt)
  call datrack.tcl
endif
free
```

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```
;  
; PUTRACK  
; put a bottle in a rack from the any safe position
```

```
*****  
USE OF PROCEDURE:
```

before calling this procedure set the variable:
 rack_type to reflect the type of bottle that is being picked up
 robot_location = the location in the rack

the following variables should be set in the gan_init.tcl procedure:

```
row_size(rack_type) = number of locations that are parallel to the track  

rack_jog(rack_type) = distance to jog down to get bottle  

track_jog(rack_type) = distance between the locations  

rack_safe$(rack_type) = safe position  

rack_im_1$(rack_type) = intermediate point #1  

rack_im_2$(rack_type)  

rack_im_3$(rack_type)  

rack_high$(rack_type) = high point names for this rack  

(the procedure adds the location number to this name so that  

the robot moves to the first location in a row and moves the  

track to the appropriate final location. So rack_high$ should  

look like: "SAM_HI_")
```

NOTES:

If there are more racks than bottle types, you can have many of these
 'es of procedures for each type. For example, create a new procedure
 called getrack1.tcl and call each of the arrays by a different name. So
 rack_high\$(rack_type) could be renamed rack1_high\$(rack_type), etc.

```
*****
```

```
if (log_robot)  

  logrobot$ = "putrack -- rack: " + numtostr$(rack_type) + " loc: " + numtostr$;  

  call logrobot.tcl  

  endif  

  if (simulate_robot)  

    if (!getting_rt)  

      call dattrack.tcl  

    endif  

    stop  

  endif  

  request "ROBOT"  

  ROBOT.speed sp_vfast  

  if(rack_type==5)  

    tum1_continue=0  

    while (!tum1_latched)  

    ~dwhile
```

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```

elseif (rack_type==5)
  tum2_continue=0
  while (!tum2_latched)
    endwhile
  endif

found = 0
robot_i = 1
while (!found)
  if (rack_location <= robot_i * row_size(rack_type))
    if ((rack_type==3) || (rack_type==4))
      ROBOT.move "rack_im"
    endif

    rack_temp$ = rack_high$(rack_type) + numtostr$(robot_i)
    ROBOT.move rack_temp$
    ROBOT.finish
    found = 1
  else
    robot_i = robot_i + 1
  endif
endwhile

ROBOT.speed sp_fast

jog_temp = track_jog(rack_type)*((row_size(rack_type)*robot_i) - rack_location)
ROBOT.joint 6,-jog_temp
ROBOT.finish

if ((rack_type==5) || (rack_type==6) || (rack_type==3))
  ROBOT.speed sp_vslow
else
  ROBOT.speed sp_slow
endif

if (rack_type==7)
  ROBOT.jog_s 0,0,(-rack_jog(rack_type)+.5)
else
  ROBOT.jog_s 0,0,-rack_jog(rack_type)
endif
ROBOT.finish
ROBOT.open
delay 500
ROBOT.speed sp_slow
ROBOT.jog_s 0,0,rack_jog(rack_type)
ROBOT.finish
ROBOT.speed sp_fast

if (!getting_rt)
  call datrack.tcl
endif

if (rack_type==5)
  tum1_continue=1

```

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```
elseif (ram_type==6)
    ram2_continue=1
endif
```

```
f2
```

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```

; Procedure: PUT_TUM
; Purpose: Put syringe in tumbler
; Author: MJB
;-
if (syr_rack[current_index]==10)
  if (syr_size[current_index]==10)
    syringe = 1
  else
    syringe = 2
  endif
  grip = 1
  nest = 1
  call gathold.tcl
  syr_rack[current_index] = 10
  syr_rackloc[current_index] = 0
  syr_grip[current_index] = 1
endif

;change grip if needed
if (syr_grip[current_index]==2)
  if (syr_size[current_index]==10)
    syringe = 1
  else
    syringe = 2
  endif
  grip = 2
  nest = 1
  c `l puthold.tcl
  c `l stopchek.tcl
  grip = 1
  nest = 1
  call gethold.tcl
  call stopchek.tcl
endif

;find next available tumbling rack space
if (syr_size[current_index]==10)
  rack_kind = 5
else
  rack_kind = 6
endif
tum_current = 0
old_tum = 1
syr_rackloc[current_index] = 0
while (syr_rackloc[current_index]==0)
  no_index = 0
  tum_current = 0
  while (!no_index)
    narrayfind tum_current,syr_rackloc(tum_current+1),old_tum
    if (tum_current==1)

```

```
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if (syr_rack(tum_current)==rack_kind)..
  no_index = 1
endif
elseif (tum_current==1)
  syr_rackloc[current_index] = old_tum
  no_index = i
endif
endwhile

old_tum = old_tum + 1
endwhile

if (syr_size[current_index]==10)
  syr_rack[current_index] = 5
else
  syr_rack[current_index] = 6
endif

;place syringe in tumbling rack
rack_type = syr_rack[current_index]
rack_location = syr_rackloc[current_index]
call putrack.tcl
call stopchek.tcl
```

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```
; Procedure: MONITOR
; Purpose: Main procedure for data input
; Author: CES

user_choice = 0
current_row = num_syringes+1
last_row = current_row
screenon "monitor"
enablekeys

running = 1
run robot.tcl
run shake.tcl

while (running)
  if (user_choice != 0)
    if (user_choice == 1 || user_choice == 2)
      ; Insert syringe(s)
      if (num_syringes >= 100)
        tellalarm "No more syringes may be added."
      else
        disablekeys
        screenhold
        call insert.tcl
        updatetable
        screenupdate
        enablekeys
      endif
    user_choice = 0
  elseif (user_choice == 3)
    disablekeys
    delete_row = current_row
    call delete.tcl
    updatetable
    screenupdate
    enablekeys
    user_choice = 0
  elseif (user_choice == 4)
    stringrequest "CALCULATING"
    call calc.tcl
    stringfree "CALCULATING"
    user_choice = 0
  elseif (user_choice == 5)
    call reagents.tcl
    user_choice = 0
  elseif (user_choice == 6)
    call amino.tcl
    user_choice = 0
  elseif (user_choice == 7)
    ; clear all syringes...only works if 'initialization = 0'
    disablekeys
    call clearall.tcl
    enablekeys
```

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```
user_choice = 0
elseif^(user_choice == 8)
  disablekeys
  call snapshot.tcl
  enablekeys
  user_choice = 0
elseif^(user_choice == 20)
  call equipinit.tcl
  screenupdate
  enablekeys
  user_choice = 0
elseif^(user_choice == 21)
  ; change protocol
  call protocol.tcl
  user_choice = 0
elseif^(user_choice == 22)
  call tasti6.tcl
  user_choice = 0
elseif^(user_choice == -1)
  ; Verify termination of system
  ask user_choice,"Are you sure you want to terminate?\n"
  if^(user_choice)
    call stopstr.tcl
    terminate
  endif
  user_choice = 0
endif
elseif^(current_col || current_row != last_row)
  if^(current_row == last_row)
    if^(current_row <= num_syringes+1 && syr_process[current_row]<=1)
      disablekeys
      screenupdate
      screenhold
      call syrinfo.tcl
      updatetable
      screenupdate
      enablekeys
    endif
  else
    last_row = current_row
  endif
  current_col = 0
endif
endwhile
screenon "logo"
initialization = 0
```

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```
Procedure : NEXTSTEP
Purpose  : Figure out the next step for a syringe
Author   : MJB,CES
Notes    : Input -- ns_process
           ns_amino
           ns_dodap$
           Output -- ns_process
           ns_amino

; If it is the end of an amino acid, figure out what the next process
; should be
if (prot_proc(ns_process) == step_nextamino)
  ns_amino = ns_amino + 1
  if (ns_amino <= couplings)
    ns_process = 2
  else
    ns_process = ns_process + 1
  endif

; If it is the Stop if no deprotection, figure out if we are done
elseif (prot_proc(ns_process) == step_stopifnofinaldep)
  if (ns_dodap$ == "Y")
    ns_process = ns_process + 1
  else
    ns_process = num_procs
  endif

; Otherwise, just add one to the process number
else
  ns_process = ns_process + 1
endif

setstringarray restart_infos[1], "", -1
savevars 7, "restart.dat"
```

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```

; Procedure : REAGENTS
; Purpose   : Allow operator to change reagents
; Author    : MJB
;= local a$,a,change
 disablekeys
; Set the colors of the volumes -- set the ones that have their required
; greater than their available to red.
 a = 1
 while (a <= 4)
   if (sol_req[a] > sol_avail[a])
     sol_color[a] = 4
   else
     sol_color[a] = 15
   endif
   a = a + 1
 endwhile
 sol_col = 0
 sol_row = 0
 screenon "reagents"
 enablekeys
 user_choice = 0
 while (user_choice != -1)

   if (sol_row)
     if (sol_col==2)
       a$ = contents$(sol_row)
       inputstring a$,"Input Probe Contents"
       if (a$ != contents$(sol_row) && a$ != "")
         contents$(sol_row) = a$
         change = 1
       endif
     elseif (sol_col==3)
       a = sol_conc(sol_row)
       inputnum a,"Input Concentration"
       if (a != sol_conc(sol_row) && a > 0)
         sol_conc(sol_row) = a
         change = 1
       endif
     elseif (sol_col==5)
       a = sol_avail(sol_row)
       inputnum a,"Input Available Volume"
       if (a != sol_avail(sol_row) && a >= 0)
         sol_avail(sol_row) = a
         if (sol_avail[sol_row] >= sol_req[sol_row])
           sol_color[sol_row] = 15
         else
           sol_color[sol_row] = 4
         endif
         change = 1
       endif
     endif
   endif

```

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```
update_table
sol_row = 0
sol_col = 0
elseif (user_choice == 1)
  savevars 4, "reagents.dat"
  user_choice = -1
elseif (user_choice == 2)
  user_choice = -1
  if (change)
    ask a, "Exit without saving?"
    if (a)
      loadvars 4, "reagents.dat"
    else
      user_choice = 0
    endif
  endif
endif
endif

endwhile

screenback
```

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```
Procedure: ROBHOME
Purpose: Home the robot
Author: MJB,CES
Notes:

local choice

request "ROBOT"
sysinit_message$ = ""
robot_ready = 1
screenupdate

; Arm Power
tell "Make sure Robot Arm Power is on."
robot_ready = robot_ready | 2
ROBOT.clearalarm
screenupdate

; Home the robot
ask choice, "Is the Robot homed?"
if (choice)
  robot_ready = robot_ready | 4
  screenupdate
  ask choice, "Is the Robot in a\nsafe position?"
  if (!choice)
    ROBOT.manualc
    sysinit_message$ = "Robot is in manual mode"
    screenupdate
    tell "The Robot is now in manual mode.\nUse teach pendant to place it\nin a
    ask choice, "Is the Robot in a safe position?\n(<No> cancels initialization)"
    if (!choice)
      robot_ready = 0
      stop
    endif
  endif
else
  /* Ask if the robot is in its HOMEPREV position */
  ask choice, "Is the Robot in its\nHOMEPREV position?"
  if (choice)
    ask choice, "Are you sure?"
  endif
  if (!choice)
    /* get the robot in its home bounds */
    ROBOT.manual
    sysinit_message$ = "Robot is in manual mode"
    screenupdate
    tell "The robot is now in manual mode.\nUse the teach pendant to place\nit in
  endif
  /* home robot */
  choice = 0
  ask choice, "Ready to home?"
  if (!choice)
    robot_ready = 0
```

```
stop -/07-
andif
sysinit message$ = "Homing sequence in progress"
disablekeys
ROBOT.command "NOMANUAL"
ROBOT.command "NOLIMP"
ROBOT.speed vsafe_speed
ROBOT.home
robot_ready = robot_ready | 4

; Move to VERIFY position
sysinit message$ = "Moving to VERIFY..."
screenupdate
ROBOT.command "NOMANUAL"
ROBOT.speed sp_med
ROBOT.move "VERIFY"
ROBOT.finish
sysinit message$ = ""
ask choice,"Is the robot at its\nVERIFY position?\n(<No> will cancel initialization)
if (!choice)
  robot_ready = 0
  stop
endif
ROBOT.open
robot_ready = robot_ready | 8
free

/* ROBOT is at VERIFY Position */
```

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```

;-----;
; Procedure: ROBOT
; Purpose: Control the robot movements
; Author: MJB,CES
; Notes:
;-----;

if (robot_running)
  stop
endif

local last_current,a
robot_running = 1
system_paused = 0
error = 0
pause_system = 1
current_index = 0
timer_start_time
time_now = start_time

while (running)
  if (initialization)
    stringrequest "USING SYRINGES"
    ; If no syringes are in the system, set the start time to zero
    if (num_syringes == 0)
      timer_start_time
      time_now = start_time
    endif

    ; check if robot has been paused
    call stopchek.tcl

    ; check if all the syringes must be cleared
    if (clear_all_syringes)
      call clearall.tcl
    endif

    ;find next syringe that robot will work on: current_index
    call whattodo.tcl

    ; while the robot has a syringe, perform the next step for the
    syringe
    while (current_index > 0)
      syr_statcolor[current_index] = 1
      last_current = current_index
      updatetable
      call dosstep.tcl
      syr_statcolor[last_current] = 0
      updatetable

```

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```
if (current_index)
    stringrequest "NEXT STEP"
    ns_process = syr_process[current_index]
    ns_amino = syr_amino_step[current_index]
    ns_dodep$ = syr_dodeprot$[current_index]
    ; Find the codes for the syringe
    bs_seq$ = syr_sequences[current_index]
    call breakseq.tcl
    call nextstep.tcl
    syr_process[current_index] = ns_process
    syr_amino_step[current_index] = ns_amino
    stringfree "NEXT STEP"
endif
savevars 5, "syringes.dat"
endwhile

stringfree "USING SYRINGES"

endif

endwhile
robot_running = 0
```

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```
Procedure: ROTATE
Purpose  : rotate syringe
Author   : MAB

;-----  
;  
;-----  
;      set    rot_time = time to rotate in seconds  
;  
;  
if (log_robot)  
  logrobotS = "rotate -- time: " + numtostr$/rot_time)  
  call logrobot.tcl  
endif  
  
if (simulate_robot)  
  stop  
endif  
  
local wait  
  
request "ROBOT"  
  
ROBOT:speed sp_slow  
timer wait  
  
ROBOT.speed 150  
while (elapsed(wait)<=rot_time)  
  P^OT.command "VIA MIXING,MIXSAFE2,MIXING"  
  L^OT.command "VIA MIXSAFE2,MIXING,MIXSAFE2"  
  ROBOT.finish  
  ; ROBOT.joint 4,90  
  ; ROBOT.joint 4,-90  
endwhile  
ROBOT.speed sp_slow  
  
free
```

;-
;- Procedure: SAFEMTR
;- Purpose : move motor to a safe position
;- Author : MJB
;-
direction = 1
motor_steps = motor_safe_step
call strkmtr.tcl

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```

; NAME: SHAKE
; PURPOSE: To Shake the appropriate tumblers
; AUTHOR: SBP
;= _____
if (shake_running)
  stop
endif

local a

shake_running = 1

tum1_latched = 1
tum2_latched = 1
tum1_continue = 1
tum2_continue = 1
while ((!initialization) && (running))
andwhile

while (running)
  if (!simulate_robot)

    if (tum1_latched && tum1_continue)
      ; Check if there is anything in the rack
      narrayfind a,syr_rack[1].5
      if (a != -1)
        ; turn tumbler 1 on
        SHARK.writebit o_tum1_clamp,1
        delay 250
        SHARK.writebit o_tum1_latch,0
        delay 500
        SHARK.writebit o_tum1_start,1
      else
        tum1_continue = 0
      endif
      tum1_latched = 0
    endif

    if (tum1_continue == 0 && tum1_latched == 0)
      ; turn tumbler 1 off
      SHARK.writebit o_tum1_latch,0
      delay 250
      SHARK.writebit o_tum1_start,1
      SHARK.readbit i_sense_tum1,a
      while ((a)
        SHARK.readbit i_sense_tum1,a
      endwhile
      SHARK.writebit o_tum1_start,0
      delay 250
      SHARK.writebit o_tum1_latch,1
      delay 250
      SHARK.writebit o_tum1_clamp,0
    endif
  endif
endif

```

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```
tum1_latched = 1
endif

if (tum2_latched && tum2_continue)
; Check if there is anything in the rack
narrayfind a,syr_rack[1],6
if (a != -1)
; turn tumbler 2 on
SHARK.writebit o_tum2_clamp,1
delay 250
SHARK.writebit o_tum2_latch,0
delay 500
SHARK.writebit o_tum2_start,1
else
tum2_continue = 0
endif
tum2_latched = 0
endif

if (tum2_continue == 0 && tum2_latched == 0)
; turn tumbler 2 off
SHARK.writebit o_tum2_latch,0
delay 250
SHARK.writebit o_tum2_start,1
SHARK.readbit i_sense_tum2,a
while (!a)
SHARK.readbit i_sense_tum2,a
endwhile
SHARK.writebit o_tum2_start,0
delay 250
SHARK.writebit o_tum2_latch,1
delay 250
SHARK.writebit o_tum2_clamp,0
tum2_latched = 1
endif

endif

andwhile
shake_running = 0
```

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```
;  
; Procedure: SNAPSHOT  
; Purpose: Take a snapshot of the syringe data  
; Author: CES  
; Notes:  
;  
local file$  
  
file$ = "snapshot.dat"  
inputstring file$,"Enter the file name:"  
if (file$ == "")  
    stop  
endif  
  
erroroff  
filenew 6,file$  
if (getstatus())  
    tellalarm "Invalid file name!"  
    stop  
endif  
erroron  
  
sysmsg$ = "Waiting for robot..."  
screenupdate  
stringrequest "SYRFILE"  
sysmsg$ = "Writing to file..."  
screenupdate  
  
sf nw = 1  
whl : (sf_row <= num_syringes)  
    call syrfile.tcl  
    sf_row = sf_row + 1  
endwhile  
  
fileclose 6  
sysmsg$ = ""  
screenupdate  
  
stringfree "SYRFILE"
```

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```
;  
; Procedure: STARTUP  
; Purpose  : startup system  
; Author   : MJB  
;=
```

```
enablekeys  
call init.tcl  
if (next_syringe <= 1)  
  screenon "logo"  
else  
  call restart.tcl  
  run monitor.tcl  
endif
```

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; Procedure: STOPCHECK
; Purpose: checks to see if pause system has been hit
; Author: MJB

```
; Free this string because it is ok to update the syringe list
stringfree "USING SYRINGES"
if (pause_system)
  if (!simulate_robot)
    request "ROBOT"
    ROBOT.manualc
    free
  endif
  system_paused = 1
  screenupdate
  while (pause_system)
  endwhile
  if (!simulate_robot)
    request "ROBOT"
    ROBOT.command "NOMANUAL"
    free
  endif
  system_paused = 0
  screenupdate
endif
; request syringe list again
stringrequest "USING SYRINGES"
```

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```

; Procedure: SYR_ASP
; Purpose  : move syringes to cup and aspirate solution
; Author   : MJB
;-

; set      cup = 1 for RGP1, 2 for RGP2
;          syringe = 1 for 10ml , 2 for 2.5ml
;          asp_amount = amount of solution to aspirate
;          air_amount = amount of air to draw in

if (log_robot)
  logrobot$ = "syringe aspirate -- cup: " + numtostr$(cup) + " syringe: " + numtostr$(syringe)
  call logrobot.tcl
  logrobot$ = "                                -- amount: " + numtostr$(asp_amount) + " air am
  call logrobot.tcl
endif

if (simulate_robot)
  stop
endif

request "ROBOT"

ROBOT.speed sp_fast
ROBOT.move "mixsafe2"
a$ = "mixs" + numtostr$(cup) + numtostr$(syringe)
ROBOT.move a$

ROBOT.speed sp_vslow
while (!disp_done)
  endwhile

ROBOT.jog_s 0,0,-4
ROBOT.finish
delay 500

/* Program to pull up syringes for solution amount */
if (syringe==1)
  motor_steps = (asp_amount+air_amount)*syrg1_cal.asp
  syr_amount[current_index] = syr_amount[current_index] + asp_amount + air_amount
else
  motor_steps = (asp_amount+air_amount)*syrg2_cal.asp
  syr_amount[current_index] = syr_amount[current_index] + asp_amount + air_amount
endif
if ((motor_steps-int(motor_steps))>=.5)
  motor_steps = int(motor_steps) + 1

```

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```
else
  motor_steps = int(motor_steps)
endif
direction = 0
call strkmtr.tcl
/*
;ROBOT.jog_s 0,0,4
;ROBOT.finish
delay 500
savevars 5,"syringes.dat"
ROBOT.speed sp_mslow
ROBOT.jog_s 0,0,4
ROBOT.finish
ROBOT.speed sp_fast
a$ = "mixs" + numtostr$(cup) + numtostr$(syringe)
ROBOT.move a$
ROBOT.move "mixsafe2"
free
```

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```
Procedure: SYR_DSP
Purpose  : move syringe to cup and dispense solution
Author   : MJB

;-----  
;  
;      set      cup = 1 for RGP1, 2 for RGP2  
;      dsp_amount = amount of solution to dispense  
;  
  
if (log_robot)  
  logrobot$ = "syringe dispense -- cup: " + numtostr$(cup) + " amount: " + numto  
  call logrobot.tcl  
endif  
  
if (simulate_robot)  
  stop  
endif  
  
request "ROBOT"  
ROBOT.speed sp_fast  
ROBOT.move "mixsafe2"  
ROBOT.speed sp_med  
a$ = "mixs" + numtostr$(cup) + numtostr$(syringe)  
ROBOT.move a$  
ROBOT.speed sp_vslow  
ROBOT.jog_s 0,0,-3.25  
ROBOT.finish  
delay 500  
  
/* Program to dispense from a syringe*/  
if (syringe==1)  
  motor_steps = dsp_amount*syr1_cal_dsp  
else  
  motor_steps = dsp_amount*syr2_cal_dsp  
endif  
if ((motor_steps-int(motor_steps))>=.5)  
  motor_steps = int(motor_steps) + 1  
else  
  motor_steps = int(motor_steps)  
endif  
direction = 1  
call strkmtr.tcl
```

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```
/*-----*/
/* Program to suck up drop from tip*/
if (syringe==1)
  motor_steps = dsp_drop_amount1*syrge1_cal_dsp
else
  motor_steps = dsp_drop_amount2*syrge2_cal_dsp
endif
if ((motor_steps-int(motor_steps))>=.5)
  motor_steps = int(motor_steps) + 1
else
  motor_steps = int(motor_steps)
endif
direction = 0
call strkmtr.tcl

/*-----*/
ROBOT.speed sp_mslow
ROBOT.jog_s 0,0,3.25
ROBOT.finish

ROBOT.speed sp_med
ROBOT.move "mixsafe2"
free
```

WO 96/22157

PCT/US96/01168

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FOCUS PAGE

WO 96/22157

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PCT/US96/01168

Title:

Apparatus and Method for Multiple Synthesis of Organic Compounds
on Polymer Support

Authors:

Krchnak et al

Attorney Docket No.:
7156-068

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```
Procedure: SYRFILE
Purpose: Write a syringe's data to a file
Author: CES
Notes: The file number will be 3 upon entry
sf_row will be the syringe to log

local a$  
  
stringformat a$,"Pepcode: #15.15s Size: #s ml",syr_pepcode$(sf_row),numtostr$(s  
fileappend 6,a$  
a$ = "Sequence: " + syr_sequence$(sf_row)  
fileappend 6,a$  
if (prot_proc(syr_process(sf_row)) != step_finished)  
    stringformat a$,"Current Amino: #2.0lf    Resin: #4.1lf    Subst: #4.2lf    Pi  
fileappend 6,a$  
if (syr_loc(sf_row))  
    stringformat a$,"Status: #13.13s Location: In Input Rack (Loc #.0lf)",pro  
elseif (syr_rack(sf_row) == 5 || syr_rack(sf_row) == 6)  
    stringformat a$,"Status: #13.13s",prot_step$(prot_proc(syr_process(sf_row))  
else  
    stringformat a$,"Status: #13.13s",prot_step$(prot_proc(syr_process(sf_row))  
endif  
fileappend 6,a$  
a$ = "Start: " + syr_datetime$(sf_row)  
fileappend 6,a$  
else  
    stringformat a$,"Resin: #4.1lf    Subst: #4.2lf    Final Deprot: #s",syr_resin  
    ``.append 6,a$  
    ` = "Start: " + syr_datetime$(sf_row) + "    Finished: " + date$() + " " + tim  
    fileappend 6,a$  
endif  
fileappend 6,""
```

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```

; Procedure: SYRINFO
; Purpose: User wants to change syringe info
; Author: CES
local a$,choice,temp,oldchoice

; change the peptide code
if (current_col == 1 && current_row <= num_syringes)
  a$ = syr_pepcodes[current_row]
  inputstring a$, "Enter the peptide's code:"
  if (a$ == "" || strlen(a$) > 8)
    tellalarm "That code is invalid."
  elseif (a$ != syr_pepcodes[current_row])
    syr_pepcodes[current_row] = a$
    savevars 5,"syringes.dat"
  endif

; change the peptide sequence
elseif (current_col == 2 && current_row <= num_syringes)
  a$ = syr_sequences[current_row]
  inputlongstring a$, "Enter the peptide's sequence:"
  bs_seq$ = a$
  call breakseq.tcl
  if (bs_error || (!couplings))
    tellalarm "That sequence is invalid."
  elseif (a$ != syr_sequences[current_row])
    syr_amino_count[current_row] = couplings
    syr_sequences[current_row] = a$
    yr_process[current_row] = 0
    alc_needed = 1
    savevars 5,"syringes.dat"
  endif

; change the syringe size
elseif (current_col == 4)
  menu choice,"Pick a size:","10 ml","2.5 ml"
  if (choice && syr_size[current_row] != 10-(7.5*(choice-1)))
    syr_size[current_row] = 10-(7.5*(choice-1))
    syr_loc[current_row] = 0
    syr_rack[current_row] = 0
    syr_rackloc[current_row] = 0
    syr_process[current_row] = 0
    savevars 5,"syringes.dat"
  endif

; change the syringes location
elseif (current_col == 5 && current_row <= num_syringes)
  choice = syr_loc[current_row]
  inputint choice,"Enter the location:"
  if (choice != syr_loc[current_row])
    if (choice)
      if (choice < 1 || choice > 30)
        tellalarm "The location must be between 1 and 30"
        sysmsg$ = ""

```

```

screenupdate
stop
endif
sysmsg$ = "Checking rack..."
screenupdate
temp = 1
while (temp <= num_syringes)
  if (syr_loc[temp] == choice && temp != current_row && syr_size[temp] ==
    tellalarm "That location is already used!"
    sysmsg$ = ""
    screenupdate
    stop
  endif
  temp = temp + 1
endwhile
sysmsg$ = ""
screenupdate
endif
if (syr_loc[current_row] == 0 && choice > 0)
  calc_needed = 1
elseif (choice == 0)
  syr_process[current_row] = 0
endif
syr_loc[current_row] = choice
savevars 5,"syringes.dat"
endif

; Change resin amount
elseif (current_col == 6)
  a = syr_resin[current_row]
  inputnum a,"Enter the resin amount:"
  if (a != syr_resin[current_row])
    syr_resin[current_row] = a
    if (syr_process[current_row] > 0)
      syr_process[current_row] = 0
      calc_needed = 1
    endif
    savevars 5,"syringes.dat"
  endif

; Change substitution amount
elseif (current_col == 7)
  a = syr_subst[current_row]
  inputnum a,"Enter the subst. amount:"
  if (a != syr_subst[current_row])
    syr_subst[current_row] = a
    if (syr_process[current_row] > 0)
      syr_process[current_row] = 0
      calc_needed = 1
    endif
    savevars 5,"syringes.dat"
  endif

; Do final deprotection?
elseif (current_col == 8)

```

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```
if (syr_c_dodeprot$[current_row] == "Y")
  syr_dodeprot$[current_row] = "N"
else
  syr_dodeprot$[current_row] = "Y"
  if
    if (syr_process[current_row] > 0)
      syr_process[current_row] = 0
      calc_needed = 1
    endif
  savevars 5, "syringes.dat"
endif
```

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```
; Procedure: SVRINIT
; Purpose: Initialize the syringe pump
; Author: MJB,CES
; Notes:
;
local choice,temp
syringe_ready = 1
screenupdate
;
; Check syringe pump power
sysinit_message$ = "Checking Syringe Pump Power"
screenupdate
call syrpower.tcl
if (!sp_power)
  syringe_ready = 0
  erroron
  stop
endif
syringe_ready = syringe_ready | 2
;
; Fill the reservoir
tell "Fill the Syringe Pump reservoir."
syringe_ready = syringe_ready | 4
screenupdate
;
; Prime the syringes
ask "choice,""Do you want to prime the syringe pumps?""
if (.choice)
  tell "Prime them now."
  tell "Turn the pumps off and then on."
endif
sysinit_message$ = "Checking Syringe Pump Power"
screenupdate
call syrpower.tcl
if (!sp_power)
  syringe_ready = 0
  erroron
  stop
endif
syringe_ready = syringe_ready | 8
screenupdate
erroron
```

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```

; Procedure: WASHING
; Purpose: : executes robot actions for a washing
; Author : MJB
;

local a,buf_place,infoindex
infoindex = 1

;find buffer in reagent table
sarrayfind buf_place,contents${1},prot_buf${syr_process[current_index]}

;if syringe just started, get from input rack
if (syr_rack[current_index]!=8&&syr_rack[current_index]!=10&&syr_rack[current_index]==10)
  rack_type = 1
else
  rack_type = 2
endif
rack_location = syr_rackloc[current_index]
call getrack.tcl
syr_grip(current_index) = 1
call stopchek.tcl
endif

;switch grip on syringe
if (syr_grip[current_index]==1||((syr_rack[current_index]==8)|| (syr_rack[current_index]==9))
  if (syr_size[current_index]==10)
    syringe = 1
  else
    syringe = 2
  endif
  grip = 1
  nest = 1
  ;if syringe in restart dont pick up
  if (syr_rack[current_index]!=8&&syr_rack[current_index]!=9)
    call puthold.tcl
    call stopchek.tcl
  endif
  if (syr_size[current_index]==10)
    syringe = 1
  else
    syringe = 2
  endif
  grip = 2
  nest = 1
  call gethold.tcl
  syr_grip[current_index] = 2
  call stopchek.tcl
endif

;squeeze out solution in syringe
if ((syr_size[current_index]==10&&syr_amount[current_index]>drop_amount1)|| (syr_size[current_index]==11&&syr_amount[current_index]>drop_amount1))
  call '1 waste.tcl

```

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```

call stopchek.tcl
endif
restart_info$[infoindex] = "Wash: Emptied syringe"
savevars 7,"restart.dat"
infoindex = infoindex + 1

;dispense buffer
restart_info$[infoindex] = "Wash: Started dispensing buffer"
savevars 7,"restart.dat"
infoindex = infoindex + 1
buf_amount = prot_vol[syr_process[current_index]]
if (syringe==2)
    buf_amount = buf_amount/division_factor
endif
buf_number = buf_place
run disp buf.tcl
sol_avail[buf_place] = sol_avail[buf_place] - buf_amount
savevars 1,"amino.dat"
if (log_robot)
    logrobots = "dispense : " + numtostr$(buf_amount) + " nozzle: " + numtostr$(bu
    call logrobot.tcl
    logrobots = "solution : " + prot_buff[syr_process[current_index]]
    call logrobot.tcl
endif
restart_info$[infoindex] = "Wash: Finished dispensing buffer"
savevars 7,"restart.dat"
infoindex = infoindex + 1

;aspirate buffer
restart_info$[infoindex] = "Wash: Started aspirating buffer"
savevars 7,"restart.dat"
infoindex = infoindex + 1
cup = 1
if (syr_size[current_index]==10)
    syringe = 1
else
    syringe = 2
endif
asp_amount = buf_amount
air_amount = prot_air[syr_process[current_index]]
if (syringe==2)
    air_amount = asp_amount/division_factor
endif
call syr.asp.tcl
restart_info$[infoindex] = "Wash: Finished aspirating buffer"
savevars 7,"restart.dat"
infoindex = infoindex + 1
call stopchek.tcl

;rotate
rot_time = 60*prot_time[syr_process[current_index]]
call rotate.tcl
call stopchek.tcl

;squeeze out solution in syringe

```

call waste._-1
-restart_info\$(infoindex) = "Wash: Emptied syringe"
savevars 7,"restart.dat"
infoindex = infoindex + 1
ca ,stopchak.tcl

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```

; Procedure: WASHING
; Purpose  : executes robot actions for a washing
; Author   : MJB
;-- 

local a,buf_place,infoindex
infoindex = 1

;find buffer in reagent table
sarrayfind buf_place,contents$[1],prot_buf$(syr_process[current_index])

;if syringe just started, get from input rack
if (syr_rack[current_index]==8&&syr_rack[current_index]==10&&syr_rack[current_index]==10)
  if (syr_size[current_index]==10)
    rack_type = 1
  else
    rack_type = 2
  endif
  rack_location = syr_rackloc[current_index]
  call getrack.tcl
  syr_grip(current_index) = 1
  call stopchek.tcl
endif

;switch grip on syringe
if (syr_grip[current_index]==1||((syr_rack[current_index]==8)|| (syr_rack[current_index]==10)))
  if (syr_size[current_index]==10)
    syringe = 1
  else
    syringe = 2
  endif
grip = 1
nest = 1
;if syringe in restart dont pick up
if (syr_rack[current_index]==8&&syr_rack[current_index]==9)
  call puthold.tcl
  call stopchek.tcl
endif
if (syr_size[current_index]==10)
  syringe = 1
else
  syringe = 2
endif
grip = 2
nest = 1
call gethold.tcl
syr_grip(current_index) = 2
call stopchek.tcl
endif

;squeeze out solution in syringe
if ((syr_size[current_index]==10&&syr_amount[current_index]>drop_amount1)|| (syr_size[current_index]==11))
  call waste.tcl

```

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```

call stopchek.tcl
endif...
restart_info${infoindex} = "Wash: Emptied syringe"
savevars 7,"restart.dat"
infoindex = infoindex + 1

;dispense buffer
restart_info${infoindex} = "Wash: Started dispensing buffer"
savevars 7,"restart.dat"
infoindex = infoindex + 1
buf_amount = prot_vol[syr_process[current_index]]
if (syringe==2)
  buf_amount = buf_amount/division_factor
endif
buf_number = buf_place
run disp_buf.tcl
sol_avail[buf_place] = sol_avail(buf_place) - buf_amount
savevars 1,"amino.dat"
if (log_robot)
  logrobot$ = "dispense : " + numtostr$(buf_amount) + " nozzle: " + numtostr$(buf_number)
  call logrobot.tcl
  logrobot$ = "solution : " + prot_buf${syr_process[current_index]}
  call logrobot.tcl
endif
restart_info${infoindex} = "Wash: Finished dispensing buffer"
savevars 7,"restart.dat"
infoindex = infoindex + 1

;aspirate buffer
restart_info${infoindex} = "Wash: Started aspirating buffer"
savevars 7,"restart.dat"
infoindex = infoindex + 1
cup = 1
if (syr_size[current_index]==10)
  syringe = 1
else
  syringe = 2
endif
asp_amount = buf_amount
air_amount = prot_air[syr_process[current_index]]
if (syringe==2)
  air_amount = asp_amount/division_factor
endif
call syr.asp.tcl
restart_info${infoindex} = "Wash: Finished aspirating buffer"
savevars 7,"restart.dat"
infoindex = infoindex + 1
call stopchek.tcl

;rotate
rot_time = 60*prot_time[syr_process[current_index]]
call rotate.tcl
call stopchek.tcl

;squeeze out solution in syringe

```

call waste.tcl
restart_info\$[infoindex] = "Wash: Emptied syringe"
savevars 7,"restart.dat"
infoindex = infoindex + 1
ca. ./stopchek.tcl

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```

;-----  

; Procedure: WASTE  

; Purpose  : move to waste and dispense liquid  

; Author   : MJB  

;-----  

if (log_robot)  

  logrobot$ = "waste : "+ numtostr$(syr_amount[current_index])  

  call logrobot.tcl  

endif  

if (simulate_robot)  

  stop  

endif  

request "ROBOT"  

ROBOT.speed sp_med  

ROBOT.move "waste"  

ROBOT.speed sp_mslow  

ROBOT.jog_s 0,0,-waste_jog  

ROBOT.finish  

/* Program to squeeze out liquid */  

if (syringe==1)  

  motor_steps = (syr_amount[current_index]+1)*syrg1_cal_dsp  

else  

  motor_steps = (syr_amount[current_index]+.25)*syrg2_cal_dsp  

endif  

if ((motor_steps-int(motor_steps))>=.5)  

  motor_steps = int(motor_steps) + 1  

else  

  motor_steps = int(motor_steps)  

endif  

direction = 1  

call strkmtr.tcl  

syr_amount[current_index] = 0  

savevars 5,"syringes.dat"  

/*-----*/  

/* Program to suck up drop */  

if (syringe==1)  

  motor_steps = drop_amount1*syrg1_cal_asp  

  syr_amount[current_index] = drop_amount1  

else  

  motor_steps = drop_amount2*syrg2_cal_asp  

  syr_amount[current_index] = drop_amount2  

endif  

if ((motor_steps-int(motor_steps))>=.5)  

  motor_steps = int(motor_steps) + 1  

else  

  motor_steps = int(motor_steps)

```

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```
endif
direction = 0
call strkmtr.tcl
/*-----*/
ROBOT.speed sp_mslow
ROBOT.jog_s 0,0,waste_jog
free
```

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```
-----  
;  
; Procedure: WHATTODO  
; Purpose : finds current_index  
; Author : RJF  
;  
  
local i, j, k, temp, temp_time, temp_busy  
local new_busy, new_step, new_amino_count, new_amino_step  
local first_temp, bail_out, new_syr_start[100], new_syr_end[100]  
  
; set the current time (leave it dummied if we are simulating times)  
if (!dont_wait)  
    time_now = elapsed(0)  
endif  
  
current_index = 0  
first_temp = 0  
bail_out = 0  
  
if (restart_index >= next_syringe)  
    tell "Make sure that the temporary nests are empty!"  
    restart_index = 0  
endif  
  
; if there are no syringes in process, start the first one or bail out  
if (next_syringe <= 1)  
    if (prot_proc(syr_process[next_syringe]) == step_ready && next_syringe <= num_  
        current_index = next_syringe  
        show "point 1"  
    e- 'if  
    s.  
endif  
  
; If one was interrupted, continue that syringe  
if (restart_index)  
    current_index = restart_index  
    show "point 2"  
    restart_index = 0  
    stop  
endif  
  
; Search through the active syringes and find the one with the shortest wait  
first_temp = 1  
i = 2  
while (i < next_syringe)  
    if (syr_processtime[i] < syr_processtime[first_temp])  
        first_temp = i  
    endif  
    i = i + 1  
andwhile  
  
; Is the syringe with the shortest wait time ready to be processed?  
if (syr_processtime[first_temp] <= time_now)  
    current_index = first_temp  
    stop
```

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```

endif

; Are there no syringes ready in the input tray?  If there are none, no
; syringe will be processed at this time
if (prot_proc(syr_process[next_syringe]) != step_ready || next_syringe > num
  if (!dont_wait)
    current_index = 0
    stop
  else
    ; Simulate the next syringe
    current_index = first_temp
    show "point"
    time_now = syr_processtime(first_temp)
    stop
  endif
endif

; Figure out if we can start the next syringe in the input rack
;

; first, set up a temp array of current tumble end-times
i = 1
while (i < next_syringe)
  temp_processtime[i] = syr_processtime[i]
  temp_amino_step[i] = syr_amino_step[i]
  temp_step[i] = syr_process[i]
  i = i + 1
endwhile

; now set up arrays of 'robot busy' time slots using all active syringes
; set the index of the START and END time arrays for robot busy periods
temp_busy = 0
robot_busy_start[0] = time_now
robot_busy_end[0] = time_now
first_temp = 1

; while we haven't examined every active syringe's future, fill in the
; busy time slots
while (first_temp)

  temp_busy = temp_busy + 1

  ; Search through the active syringes and find the one with the shortest wait
  ; that hasn't been processed to its finish step yet
  first_temp = 0
  i = 1
  while (i < next_syringe)
    if (prot_proc(temp_step[i]) != step_finished)
      if (!first_temp)
        first_temp = i
      elseif (temp_processtime[i] < temp_processtime[first_temp])
        first_temp = i
      endif
    endif
  endwhile

```

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```

i = i + 1
endwhile

; If we found a syringe that hasn't been processed to the end, process its
; next steps
if (first_temp)
  ; add up the adjacent robot move-times for that syringe
  temp = first_temp
  ; the START of these robot moves
  robot_busy_start[temp_busy] = temp_processtime[temp]
  temp_step[temp] = temp_step[temp] + 1
  temp_time = temp_processtime[temp]
  while (!(prot_choice[prot_proc[temp_step[temp]]] & param_stop))
    ;first, check if we are starting another amino
    if (prot_proc[temp_step[temp]] == step_nextamino)
      if (temp_amino_step[temp] < syr_amino_count[temp])
        temp_amino_step[temp] = temp_amino_step[temp] + 1
        temp_step[temp] = 1
      else
        temp_step[temp] = temp_step[temp] + 1
      endif
    elseif (prot_proc[temp_step[temp]] == step_stopifnofinaldep)
      if (syr_dodeproto[temp] == "y")
        temp_step[temp] = temp_step[temp] + 1
      else
        temp_step[temp] = num_procs
      endif
    else
      temp_step[temp] = temp_step[temp] + 1
      temp_time = temp_time + prot_robottime[temp_step[temp]]
    endif
  endwhile
  robot_busy_end[temp_busy] = temp_time           ;the END of thes robot moves

  ; re-assign its NEXT scheduled tumble end-time
  if (prot_proc[temp_step[temp]] != step_finished)
    temp_processtime[temp] = temp_time + (prot_time[temp_step[temp]] * 60)
  endif
endif
endwhile

; Now calculate the time slots needed by the next syringe in the input rack
new_step = 1
temp_time = time_now
new_busy = 0
new_amino_step = 1

while (prot_proc[new_step] != step_finished)

  new_busy = new_busy + 1
  ; the START of these robot moves
  new_syr_start[new_busy] = temp_time
  while (!(prot_choice[prot_proc[new_step]] & param_stop))
    ;first, check if we are starting another amino

```

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```

if (pro_proc[new_step] == step_nxtamino)
  if (new_amino_step < syr_amino_count[next_syringe])
    new_amino_step = new_amino_step + 1
    new_step = 1
  else
    new_step = new_step + 1
  endif
elseif (prot_proc[new_step] == step_stopifnofinaldep)
  if (syr_dodeprotS[next_syringe] == "Y")
    new_step = new_step + 1
  else
    new_step = num_procs
  endif
else
  new_step = new_step + 1
  temp_time = temp_time + prot_robottime(new_step)
endif
endwhile
; the END of these robot moves
new_syr_end[new_busy] = temp_time

; re-assign its NEXT scheduled tumble end-time
if (prot_proc[new_step] != step_finished)
  temp_time = temp_time + (prot_time(new_step) * 60)
  new_step = new_step + 1
endif
endwhile

; Now compare the time line of the active syringes and the new syringe
; and see if the new syringe fits
i = 1
j = 0
if (new_syr_end[i] < robot_busy_start[i]) ;the first block of moves is clear
  i = 2
  while ((i <= new_busy) && (!bail_out) && (j <= temp_busy))
    if ((new_syr_start[i] >= robot_busy_end[j]) && (new_syr_end[i] <= robot_busy_end[j]))
      i = i + 1
    elseif ((new_syr_start[i] >= robot_busy_start[j]) && (new_syr_start[i] < robot_busy_end[j]))
      bail_out = i
      k = j
    elseif ((new_syr_end[i] > robot_busy_start[j]) && (new_syr_end[i] <= robot_busy_end[j]))
      bail_out = i
      k = j
    elseif ((robot_busy_start[j] >= new_syr_start[i]) && (robot_busy_start[j] < new_syr_end[i]))
      bail_out = i
      k = j
    elseif ((robot_busy_end[j] > new_syr_start[i]) && (robot_busy_end[j] <= new_syr_end[i]))
      bail_out = i
      k = j
    else
      j = j + 1
    endif

```

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```
    andwhile
else
  bail_out = 5
endif
;if 'next_syringe' not on hold, and there is one in the input rack, get it
if (!bail_out)
  current_index = next_syringe
  show "point 4"
else
  ; if don't want to wait and there is a syringe in process
  current_index = 0
  if (dont_wait)
    time_now = time_now + 60
  endif
endif
```

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```
=====
; Procedure: FINDTOP
; Purpose   : turn on motor until sensor is triggered
; Author    : MJB
=====

if (simulate_robot)
  stop
endif

;load zero into plc counter register
SHARK.writebit o_clear_counter,1
delay 100
SHARK.writebit o_clear_counter,0
=====

;set counter enable
SHARK.writebit o_start_counter,1
=====

;set direction to forward and turn on motor (motor will turn off
automatically)
SHARK.writebit 224,1
delay 500
SHARK.writebit 401,1
=====

;wait for syringe to be sensed
SHARK.readbit i_sense_syringe,a
timer findtop_time
while (!a)
  SHARK.readbit i_sense_syringe,a
  if (elapsed(findtop_time)>13)

    ;stop motor
    SHARK.writebit 401,0
    delay 500

    ;home motor
    call homemtr.tcl
    while (!home_done)
    endwhile
    delay 250

    ;load zero into plc counter register
    SHARK.writebit o_clear_counter,1
    delay 100
    SHARK.writebit o_clear_counter,0
=====

;call error
error_code = 5
call error.tcl
```

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```
;restart timer
timer findtop_time

;set counter enable
SHARK.writebit o_start_counter,1
;=====

;start motor to find top of syringe
SHARK.writebit 224,1
delay 500
SHARK.writebit 401,1

endif
endwhile
;=====

;read the number of counts to reach the syringe
SHARK.readctr i_motor_pulses,motor_pulses
show "motor pulses = " + numtostr$(motor_pulses)
;=====

;disable counter
SHARK.writebit o_start_counter,0
=====
```

CLAIMS:

1. A system for the solid phase synthesis of multiple species of organic compounds each formed by repeated synthetic cycles of synthetic steps, said system comprising:
 - 5 a computer for processing a program of instructions correlated to predetermined synthetic cycles for the synthesis of each of said multiple species;
 - 10 an automated robot responsive to said computer, said automated robot operative to cause said synthesis steps to be performed in accordance with the synthetic cycles of each of said multiple species; and
 - 15 a timing protocol, implemented by said program of instruction and executed by said computer, for directing synthetic steps of at least two different species to be performed concurrently.
- 20 2. The system of claim 1 wherein each of said species has an associated sequence specific timing protocol, the compilation of all sequence specific timing protocols of species currently under synthesis being a cumulative remaining timing protocol, said system further including means for determining whether
- 25 25 there is a timing conflict between the sequence specific timing protocol of a new desired species and the cumulative remaining timing protocol.
- 30 3. The system of claim 1 wherein said synthetic steps include the steps of washing, adding deprotection reagents, deprotection, adding coupling reagents and coupling.
- 35 4. The system of claim 1 wherein said synthetic steps include active and passive synthetic steps, said

timing protocol directing said active steps within a first synthesis of a first species to be performed concurrently with passive steps within a second synthesis of a second species.

5

5. The system of claim 1 wherein said organic compounds includes peptides.

6. The system of claim 1 further comprising:
10 a first set of a plurality of syringes, each syringe containing resin for repeatably coupling compounds to a solid support so as to synthesize a first species; and

15 a second set of a plurality of syringes, each syringe containing a desired compound that is to be coupled to the solid support during one of said synthetic cycles.

7. The system of claim 6 wherein said compound
20 that is to be coupled is an amino acid for the synthesis of a peptide.

8. The system of claim 7 wherein said solid phase synthesis is a Merrifield solid phase peptide
25 synthesis.

9. The system of claim 1 wherein said automated robot includes
30 a gripper arm responsive to said computer, said gripper arm selectively positioning and manipulating syringes from said first and second sets of a plurality of syringes to thereby aspirate or dispense solvents and regents required within said synthetic cycles.

35

10. The system of claim 1 further comprising a database containing parameter variables required for the synthesis of said multiple species of organic compounds, said database including the characteristic 5 sequence of the repeated synthetic cycles for each of said multiple species.

11. A system for the solid phase synthesis of multiple peptides each formed by repeated synthetic 10 cycles of synthetic steps, said system comprising:
a first set of syringes each holding a solid support;
a second set of syringes each holding a desired amino acid, said first set of syringes serving as the 15 reaction vessels for coupling desired amino acids from said second set of syringes to the solid supports;
a computer for processing a program of instructions correlated to predetermined synthetic cycles for the synthesis of multiple peptides; and
20 an automated robot responsive to said computer, said automated robot operatively coupled to said first and second sets of syringes for aspirating and dispensing reagents so as to cause said repeated synthesis cycles to be performed in accordance with a
25 desired peptide synthesis to thereby repeatably couple a desired amino acid to a solid support, said repeated synthesis cycles including the synthetic steps of washing, adding deprotection reagents, deprotection, adding coupling reagents and coupling,
30 said repeated synthesis cycles performed in accordance with a timing protocol wherein said washing, adding deprotection reagents or adding coupling reagents is performed concurrently with said deprotection or coupling for different peptide
35 syntheses.

12. The system of claim 11 wherein said first set of syringes is made of polypropylene.

13. The system of claim 11 wherein each of said 5 first set of syringes includes a solid phase retaining device

14. The system of claim 13 wherein said solid phase retaining device is a frit.

10

15. The system of claim 11 wherein said solid support comprises a resin selected from the group of polystyrene and polyethylene glycol.

15

16. The system of claim 11 where said automated robot includes an arm operatively connected to said robot so as to manipulate each of said first and second sets of syringes.

20

17. The system of claim 16 wherein said first and second sets of syringes each includes a plunger operatively coupled thereto, said plunger movable by said arm of said automated robot to thereby aspirate or dispense reagents.

25

18. The system of claim 17 wherein the content amount of reagents in each of said syringes is determined by the plunger position of the corresponding syringe.

30

19. The system of claim 11 further including an optical sensor responsive to the movement of said first and second sets of syringes, said optical sensor confirming the positioning of said first and second 35 sets of syringes.

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20. The system of claim 11 wherein said synthesis of peptides employs Fmoc/tBu chemistry.

21. The system of claim 11 further comprising 5 piston pumps and delivery cups, said piston pumps delivering solvents and reagents to said delivery cups from which said first and second sets of syringes dispense or aspirate said solvents or reagents.

10 22. The system of claim 11 further including a database containing parameter variables required for the synthesis of the multiple peptides.

15 23. A process for the solid phase automated synthesis of multiple species of organic compounds formed by repeated synthetic cycles of synthetic steps, said process comprising the steps of:

20 a) initiating a synthetic step in a synthetic cycle of a species;
b) determining if the time for said synthetic step of step a) is sufficient for initiating a synthetic step in the synthetic cycle of a different species, and if so,
c) initiating a synthetic step in the synthetic 25 cycle of said different species; and
d) repeating steps a), b) and c) until said multiple species are synthesized.

30 24. The process of claim 23 wherein said synthetic steps include washing, deprotection and coupling for the synthesis of multiple peptides.

35 25. The process of claim 24 wherein said deprotection and coupling are performed in a plurality of syringes which serve as reaction vessels.

26. A process for the automated solid phase synthesis of multiple peptides formed by repeated cycles of washing, adding deprotection reagents, deprotection, adding coupling reagents and coupling so

5 as to repeatably couple amino acids to a solid support, said process comprising the steps of:

a) filling a first set of syringes, each with a resin solid support;

10 b) filling a second set of syringes, each with a desired amino acid;

c) washing one of said first set of syringes with a first solution;

15 d) adding deprotection solution to the syringe of step d) to initiate deprotection;

e) while deprotection of step e) is proceeding repeating steps d) and e) if the time for performing those steps is less than the time required for deprotection, otherwise proceeding with step g);

20 f) adding coupling solution to the syringe of step d) to initiate coupling to thereby couple a desired amino acid to the solid support; and

g) while coupling of step g) is proceeding repeating steps f) and g) if the time for performing those steps is less than the time for coupling,

25 h) while coupling of step g) is proceeding repeating steps f) and g) if the time for performing those steps is less than the time for coupling,

otherwise proceeding with steps d) and e) until the time for coupling expires.

27. The process of claim 26 wherein steps a) through h) are repeated until a peptide is

30 synthesized.

28. The process of claim 26 further comprising the step of washing each of said first set of syringes of step d) prior to adding coupling solution.

29. The process of claim 26 wherein the system
is automated through the use of a robot, said robot
adding coupling and deprotection solution by
manipulating the syringes so as to aspirate and
5 dispense reagents.

30. The process of claim 26 wherein the first
solution is dimethylformamide.

10 31. The process of claim 26 wherein the
deprotection solution is piperidine/DMF.

32. The process of claim 26 wherein the coupling
solution is a solution of DIC/HOBt.

15 33. The process of claim 26 further comprising
the step of interactively prompting a user for
parameter variables thereby forming a database
required for the synthesis of the multiple peptides,
20 said database including the characteristic amino acid
sequence of each of the multiple peptides.

34. The process of claim 26 further comprising
the step of adding or deleting peptide sequences to a
25 list of peptides to be synthesized.

35. A process for the solid phase automated
synthesis of multiple species of organic compounds
formed by repeated synthetic cycles of synthetic
30 steps, said process comprising the steps of:
a) determining a sequence specific timing
protocol associated with a desired species to be
synthesized, said sequence specific timing protocol
including when each synthetic step for the desired
35 species occurs temporally;

b) determining the cumulative remaining timing protocol of species currently under synthesis, said cumulative remaining timing protocol including when each synthetic step for the species currently under 5 synthesis occurs temporally; and

c) determining whether a timing conflict exists between said sequence specific timing protocol and said cumulative remaining timing protocol, a timing conflict occurring when one synthetic step for the 10 desired species to be synthesized cannot be performed concurrently with the synthetic steps of species currently under synthesis.

36. The process of claim 35 further comprising 15 the step of time shifting the synthesis initiation of the desired species to be synthesized so as to resolve the time conflict.

37. The process of claim 35 wherein a time 20 conflict occurs when an active synthetic step of the desired species to be synthesized is temporally coincident with any active synthetic steps for the species currently under synthesis.

25 38. The process of claim 35 wherein said organic compounds includes peptides.

39. The process of claim 35 further comprising 30 the step of entering parameter variables required for the synthesis of the organic compounds.

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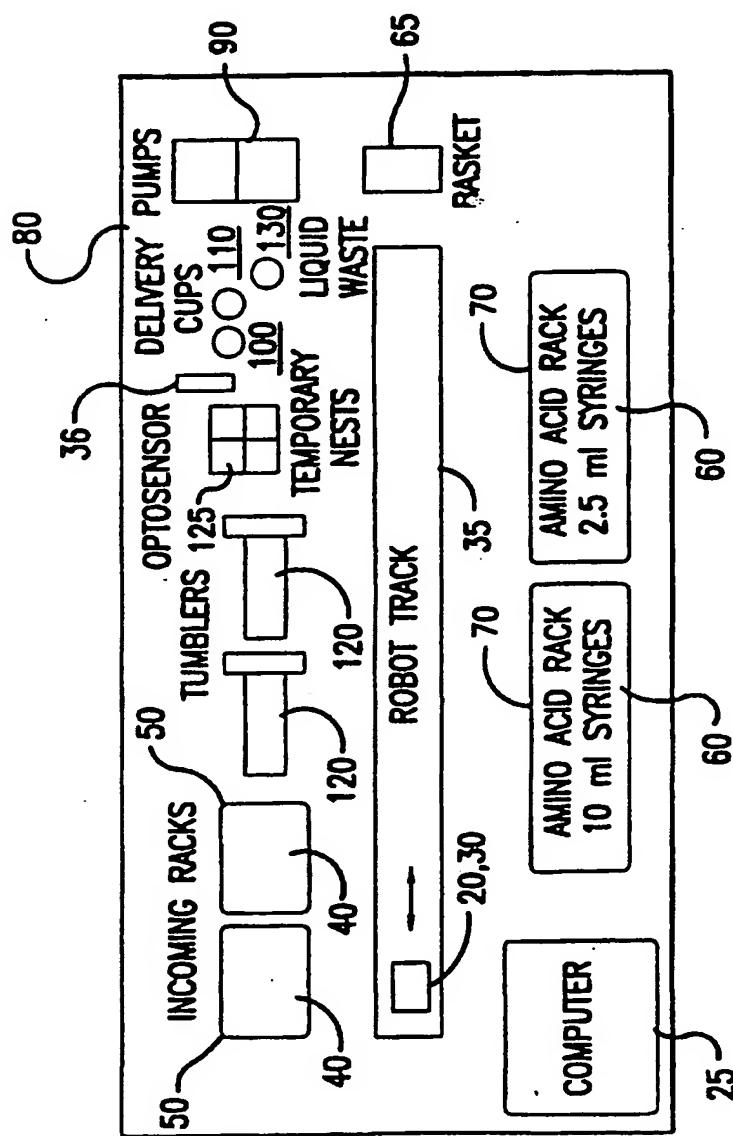


FIG. 1

10

SUBSTITUTE SHEET (RULE 26)

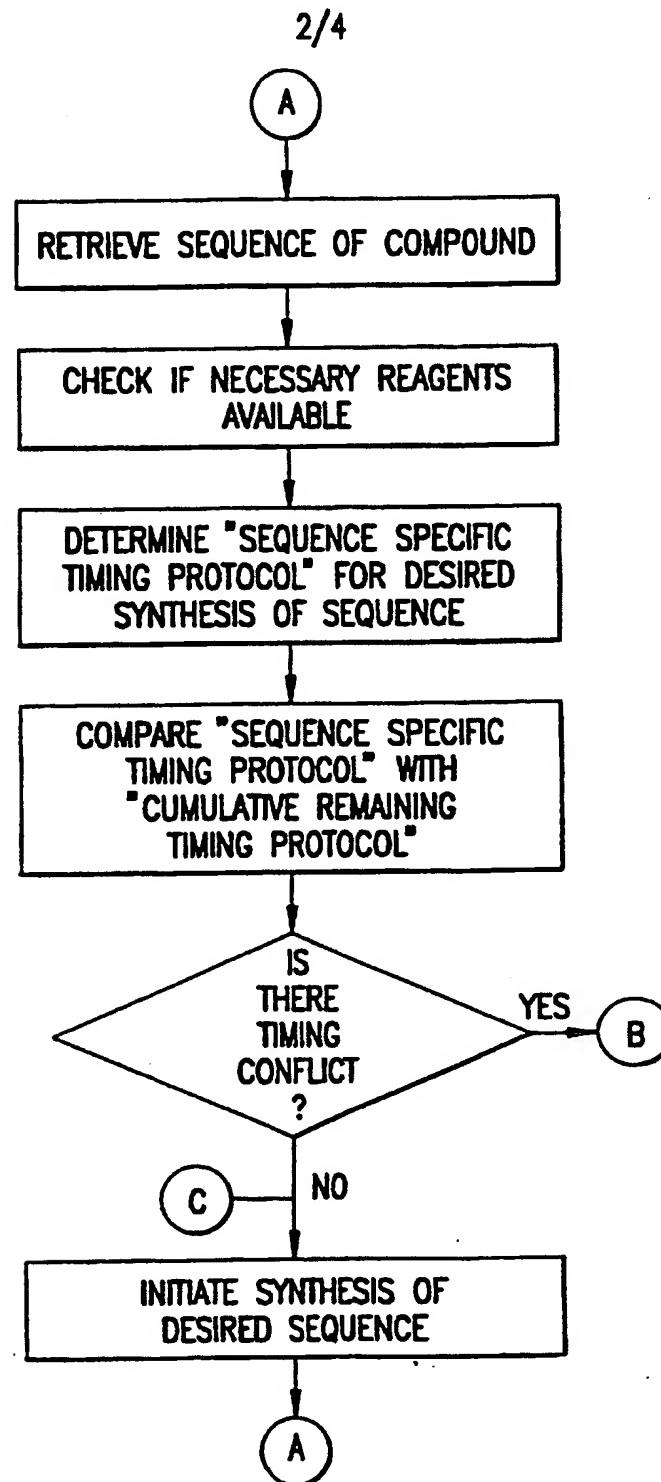


FIG. 2A
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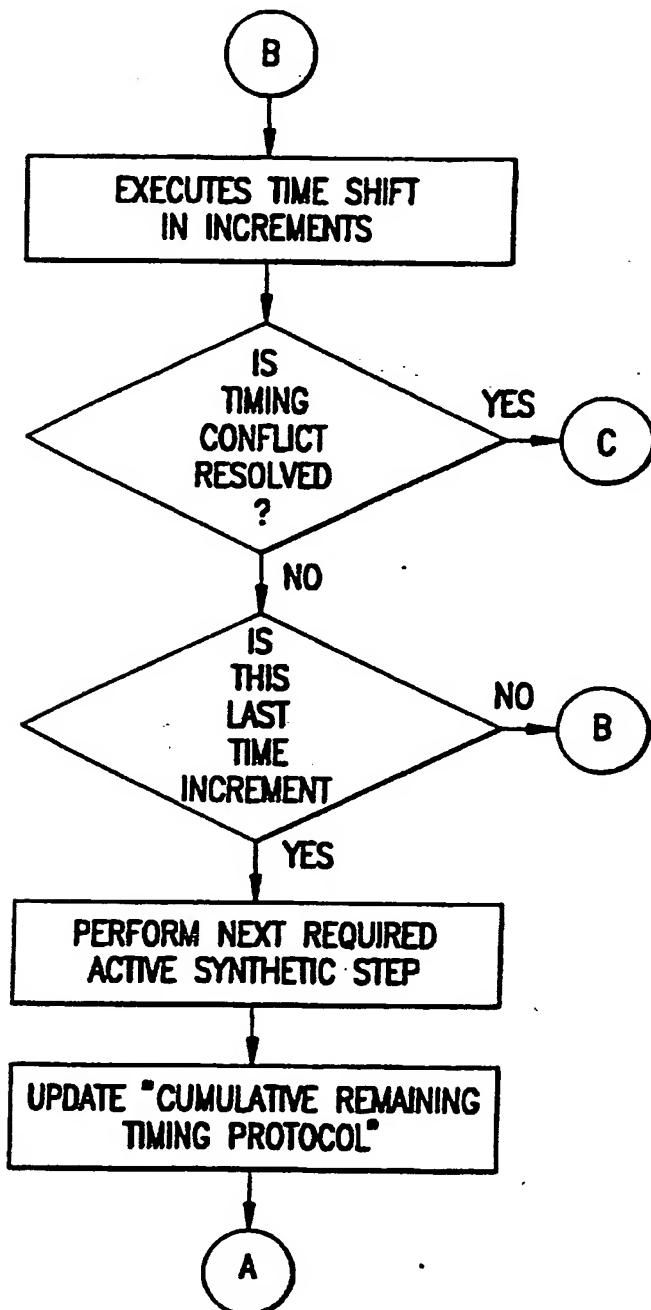


FIG. 2B
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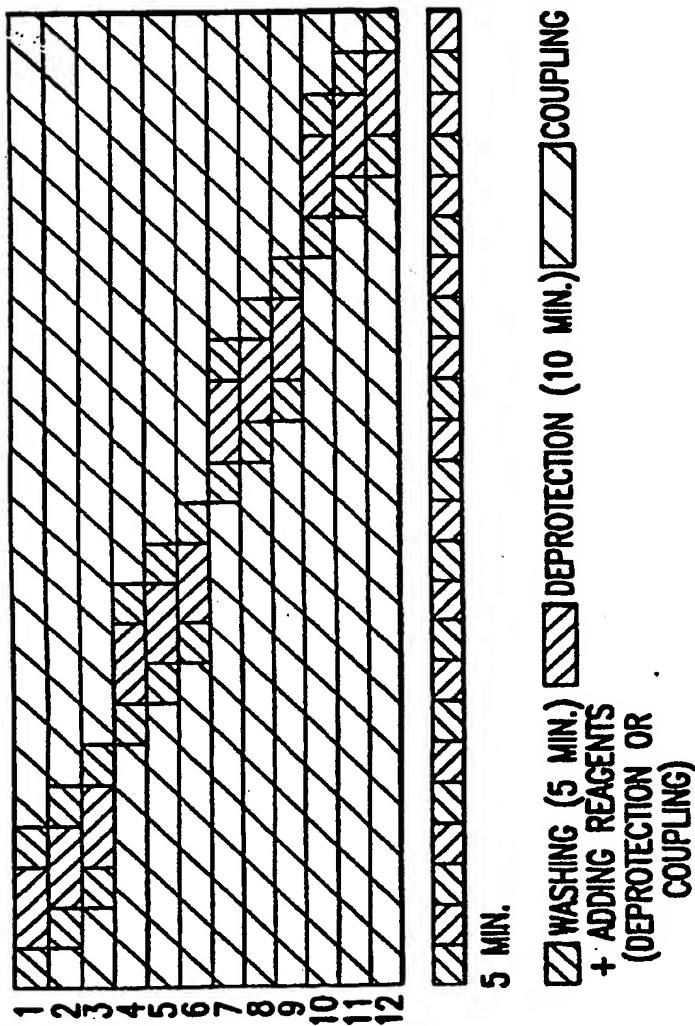


FIG. 3

PEPTIDE SYNTHESIS NO.

SUBSTITUTE SHEET (RULE 26)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US96/01168

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :Please See Extra Sheet.
 US CL :422/116; 525/54.11; 530/334; 935/88
 According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
 U.S. 395/904, 906; 422/116; 525/54.1, 54.11; 528/312, 328; 530/334, 810; 935/88

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
 APS, DIALOG
 search terms: peptide, Merrifield, robot, computer, automated, programmable, simultaneous, concurrent

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US, A, 5,147,608 (HUDSON ET AL) 15 September 1992.	1-39
X	US, A, 5,368,823 (MCGRAW ET AL) 29 November 1994, see column 2, lines 3-8 and 47-54, column 4, lines 38-42 and 66-68, column 7, line 38 - column 8, line 34, column 9, line 51 - column 10, line 2, and Table 4.	1, 3-5, 10
A	EP, A, 0 529 504 (SHIMADZU CORPORATION) 03 March 1993.	1-39
A	Biochemical Society Transactions, Volume 20, issued 1992, Fox, "Automatic multiple peptide synthesis", pages 851-853.	1-39

Further documents are listed in the continuation of Box C.

See patent family annex.

• Special categories of cited documents:	
• "A" document defining the general state of the art which is not considered to be of particular relevance	"T" later documents published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
• "E" earlier documents published on or after the international filing date	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
• "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reasons (as specified)	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
• "O" document referring to an oral disclosure, use, exhibition or other means	"Z" document member of the same patent family
• "P" document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

09 APRIL 1996

Date of mailing of the international search report

13 MAY 1996

Name and mailing address of the ISA/US
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US96/01168

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Tetrahedron, Volume 45, Number 24, issued 1989, Schnorrenberg et al, "Fully Automatic Simultaneous Multiple Peptide Synthesis In Micromolar Scale - Rapid Synthesis Of Series Of Peptides For Screening In Biological Assays", pages 7759-7764, see page 7759, sixth paragraph, page 7761, first and second paragraphs, Tables 1 and 2, and Figure 1.	1, 3-5, 10
A	International Journal Of Peptide And Protein Research, Volume 40, issued 1992, Zuckermann et al, "Design, construction and application of a fully automated equimolar peptide mixture synthesizer", pages 497-506.	1-39

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US96/01168

A. CLASSIFICATION OF SUBJECT MATTER:

IPC (6):

B01J 8/02; C07K 1/04, 1/06, 1/08, 1/10; C08F 283/00; C08G 69/10; G05B 13/00, 19/402

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